(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 May 2022 (12.05.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/099159 A1

(51) International Patent Classification:
C12N 15/11 (2006.01) *C07H 21/02* (2006.01)
C12N 9/22 (2006.01)

(21) International Application Number:
PCT/US2021/058495

(22) International Filing Date:
08 November 2021 (08.11.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/111,079	08 November 2020 (08.11.2020)	US
63/175,036	14 April 2021 (14.04.2021)	US
63/188,415	13 May 2021 (13.05.2021)	US
63/196,178	02 June 2021 (02.06.2021)	US
63/248,520	26 September 2021 (26.09.2021)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

WO 2022/099159 A1

(54) Title: OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

(57) Abstract: Among other things, the present disclosure provides oligonucleotides and compositions thereof. In some embodiments, provided oligonucleotides and compositions are useful for adenosine modification. In some embodiments, the present disclosure provides methods for treating various conditions, disorders or diseases that can benefit from adenosine modification.

[Continued on next page]

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

OLIGONUCLEOTIDE COMPOSITIONS AND METHODS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to one or more priority applications including United States Provisional Application Nos. 63/111,079, filed November 8, 2020, 63/175036, filed April 14, 2021, 63/188,415, filed May 13, 2021, 63/196,178, filed June 2, 2021, and 63/248,520, filed September 26, 2021. The entirety of each of the priority applications is incorporated herein by reference.

BACKGROUND

[0002] Oligonucleotides are useful in various applications, e.g., therapeutic, diagnostic, and/or research applications. For example, oligonucleotides targeting various genes can be useful for treatment of conditions, disorders or diseases related to such target genes.

SUMMARY

[0003] Among other things, the present disclosure provides designed oligonucleotides and compositions thereof which oligonucleotides comprise modifications (e.g., modifications to nucleobases sugars, and/or internucleotidic linkages, and patterns thereof) as described herein. In some embodiments, technologies (compounds (e.g., oligonucleotides), compositions, methods, etc.) of the present disclosure (e.g., oligonucleotides, oligonucleotide compositions, methods, etc.) are particularly useful for editing nucleic acids, e.g., site-directed editing in nucleic acids (e.g., editing of target adenosine). In some embodiments, as demonstrated herein, provided technologies can significantly improve efficiency of nucleic acid editing, e.g., modification of one or more A residues, such as conversion of A to I. In some embodiments, the present disclosure provides technologies for editing (e.g., for modifying an A residue, e.g., converting an A to I) in an RNA. In some embodiments, the present disclosure provides technologies for editing (e.g., for modifying an A residue, e.g., converting an A to an I) in a transcript, e.g., mRNA. Among other things, provided technologies provide the benefits of utilization of endogenous proteins such as ADAR (Adenosine Deaminases Acting on RNA) proteins (e.g., ADAR1 and/or ADAR2), for editing nucleic acids, e.g., for modifying an A (e.g., as a result of G to A mutation). Those skilled in the art will appreciates that such utilization of endogenous proteins can avoid a number of challenges and/or provide various benefits compared to those technologies that require the delivery of exogenous components (e.g., proteins (e.g., those engineered to bind to oligonucleotides (and/or duplexes thereof with target nucleic acids) to provide desired activities), nucleic acids encoding proteins, viruses, etc.).

[0004] Particularly, in some embodiments, oligonucleotides of provided technologies comprise useful sugar modifications and/or patterns thereof (e.g., presence and/or absence of certain modifications), nucleobase modifications and/or patterns thereof (e.g., presence and/or absence of certain modifications), internucleotidic linkages modifications and/or stereochemistry and/or patterns thereof [e.g., types, modifications, and/or

configuration (Rp or Sp) of chiral linkage phosphorus, etc.], etc., which, when combined with one or more other structural elements described herein (e.g., additional chemical moieties) can provide high activities and/or various desired properties, e.g., high efficiency of nucleic acid editing, high selectivity, high stability, high cellular uptake, low immune stimulation, low toxicity, improved distribution, improved affinity, etc. In some embodiments, provided oligonucleotides provide high stability, e.g., when compared to oligonucleotides having a high percentage of natural RNA sugars utilized for adenosine editing. In some embodiments, provided oligonucleotides provide high activities, e.g., adenosine editing activity. In some embodiments, provided oligonucleotides provide high selectivity, for example, in some embodiments, provided oligonucleotides provide selective modification of a target adenosine in a target nucleic acid over other adenosine in the same target nucleic acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 fold or more modification at the target adenosine than another adenosine, or all other adenosine, in a target nucleic acid).

[0005] Among other things, the present disclosure provides designed oligonucleotides and compositions of improved properties and/or activities compared to reference oligonucleotides and compositions (e.g., those described herein or reported in the art). For example, in some embodiments, as demonstrated herein provided oligonucleotide and compositions can provide improved stability, pharmacokinetic properties, pharmacodynamic properties and/or improved activities (e.g., for A-to-I editing). Various designed oligonucleotides and compositions are described herein. For example, in some embodiments, the present disclosure provides oligonucleotides and compositions thereof, including chirally controlled oligonucleotide compositions thereof, wherein the oligonucleotides comprise several (e.g., 1, 2, 3, 4, or 5 or more; in some embodiments, 3 or more) nucleosides independently comprising sugar modifications (e.g., 2'-OR modifications wherein R is optionally substituted C_{1-6} alkyl (e.g., 2'-OMe, 2'-MOE, etc.,), bicyclic sugars (e.g., LNA sugars, cEt sugars, etc.)) at their 5'- and 3'-ends. In some embodiments, the first several (e.g., 1, 2, 3, 4, or 5 or more; in some embodiments, 3 or more) nucleosides and/or the last several (e.g., 1, 2, 3, 4, or 5 or more; in some embodiments, 3 or more) nucleosides independently comprise sugar modifications. In some embodiments, the first 3 or more and the last 3 or more nucleosides independently comprise sugar modifications. In some embodiments, one or more internucleotidic linkages bonded to such nucleosides are non-negatively charged internucleotidic linkage such as phosphoryl guanidine internucleotidic linkages like n001. In some embodiments, both the first and the last internucleotidic linkages are independently non-negatively charged internucleotidic linkages. In some embodiments, both the first and the last internucleotidic linkages are independently phosphoryl guanidine internucleotidic linkages. In some embodiments, both the first and the last internucleotidic linkages are independently n001. In some embodiments, they are both chirally controlled and are *R*p. In some embodiments, an oligonucleotide comprises a nucleoside N_0 which comprises a natural DNA sugar (two 2'-H), a natural RNA sugar or a 2'-F modified sugar. In some embodiments, N_0 is a nucleoside opposite to a target adenosine when an oligonucleotide is utilized for adenosine editing. In some embodiments, sugar of N_0 is a natural DNA sugar. In some embodiments, sugar of N_1 ("+" or nothing before

a number indicates counting toward the 5'-direction (5' …$N_1N_0N_{-1}$… 3')) is a 2'-Fmodified sugar, a natural DNA sugar, or a natural RNA sugar. In some embodiments, sugar of N_1 is a DNA sugar. In some embodiments, sugar of N_{-1} ("-" indicates counting toward the 3'-direction (5' …$N_1N_0N_{-1}$… 3')) is a 2'-F modified sugar, a natural DNA sugar, or a natural RNA sugar. In some embodiments, sugar of N_{-1} is a DNA sugar. In some embodiments, sugar of N_{-3} is a 2'-F modified sugar. In some embodiments, between N_2 and their 5'-ends oligonucleotides comprise multiple 2'-F modified sugars and multiple 2'-modified sugars (e.g., 2'-OR modified sugars wherein R is optionally substituted C_{1-6} alkyl, bicyclic sugars such as LNA sugars, cEt sugars, etc.). In some embodiments, oligonucleotides comprise one or more (e.g., 1-20, 1-15, 1-10, 2-15, 2-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) 2'-F blocks and one or more (e.g., 1-20, 1-15, 1-10, 2-15, 2-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) separating blocks from N_2 to their 5'-ends (e.g., first domains and first subdomains of second domains combined when first subdomains end with and include N_2), wherein each nucleoside in a 2'-F block independently comprises a 2'-F modification, each nucleoside in a separating block independently comprises no 2'-F modification, and each block independently comprises one or more (e.g., 1-20, 1-15, 1-10, 2-15, 2-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) nucleosides. In some embodiments, there are two or more such 2'-F blocks and two or more such separating blocks. In some embodiments, one or more or all such separating blocks are independently bonded to two 2'-F blocks. In some embodiments, each nucleoside in one or more or all separating blocks independently comprise a 2'-OR modification wherein R is optionally substituted C_{1-6} alkyl or is a bicyclic sugar such as a LNA sugar, a cEt sugar, etc. In some embodiments, each nucleoside in one or more or all separating blocks independently comprise a 2'-OR modification wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, each nucleoside in one or more or all separating blocks independently comprise a 2'-OMe or 2'-MOE modification. In some embodiments, each of such 2'-F and separating blocks independently comprises 1, 2, 3, 4 or 5 nucleosides. In some embodiments, nucleosides close to N_0, e.g., N_2, N_1, N_0, N_{-1}, N_{-2}, etc., do not contain large 2'-modificatoins such as 2'-MOE. In some embodiments, sugars of N_2, N_1, N_0, N_{-1}, and N_{-2} are independently natural DNA sugar, 2'-F modified sugar, or 2'-OMe modified sugar. In some embodiments, sugars of N_1, N_0, N_{-1} are each a natural DNA sugar. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled.

[0006] In some embodiments, the present disclosure provides an oligonucleotide comprising a first domain and a second domain, wherein the first domain comprises one or more 2'-F modifications, and the second domain comprises one or more sugars that do not have a 2'-F modification. In some embodiments, a provided oligonucleotide comprises one or more chiral modified internucleotidic linkages. In some embodiments, the present disclosure provides an oligonucleotide comprising:

(a) a first domain; and

(b) a second domain,

wherein the first domain comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,

19, or 20 or more sugars comprising a 2'-F modification and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more sugars each independently comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2,-MOE, 2'-O−L^B−4' wherein L^B is optionally substituted −CH_2−, etc.); and

the second domain comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more sugars each independently comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2,-MOE, 2'-O−L^B−4' wherein L^B is optionally substituted −CH_2−, etc.).

[0007] In some embodiments, the present disclosure provides an oligonucleotide comprising:

(a) a first domain; and

(b) a second domain,

wherein about 20%-80% (e.g., about 25%-80%, 30%-80%, 35%-80%, 40%-80%, 40%-70%, 40%-60%, 50%-80%, 50%-75%, 50%-60%, 55%-80%, 60-80%, or about 50%,55%, 60%, 65%, 70%, 75%, or 80%) of all sugars of the first domain comprises a 2'-F modification, and about 20%-70% (e.g., about 20%-60%, 20%-50%, 30%-60%, 30%-50%, 40%-50%, or about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60%) of all sugars of the first domain independently comprises a 2'-OR modifications wherein R is not −H (e.g., 2'-OMe, 2,-MOE, 2'−O−L^B−4' wherein L^B is optionally substituted −CH_2−, etc.); and

the second domain comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more modified sugars comprising no 2'-F modification, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all sugars of the second domain comprise no 2'-F modification.

[0008] In some embodiments, a second domain comprises or consists of a first subdomain, a second subdomain and a third subdomain as described herein. In some embodiments, a first subdomain comprises one or more (e.g., 1-10, 1-5, 1-3, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars each independently comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2,-MOE, 2'-O−L^B−4' wherein L^B is optionally substituted −CH_2−, etc.). In some embodiments, there are more such sugars in a first subdomain than 2'-F modified sugars. In some embodiments, none of sugars in a second subdomain contain any 2'-OR modifications wherein R is optionally substituted C_{1-6} aliphatic or 2'−O−L^B−4'). In some embodiments, each sugar of a second subdomain is independently a natural DNA sugar, a natural RNA sugar or a 2'-F modified sugar. In some embodiments, each sugar of a second subdomain is independently a natural DNA sugar or a natural RNA sugar. In some embodiments, each sugar of a second subdomain is independently a natural DNA sugar or a 2'-F modified sugar. In some embodiments, each sugar of a second subdomain is independently a natural DNA sugar. In some embodiments, there are three nucleosides in a second subdomain. In some embodiments, when binding to a target the second nucleoside the three is opposite to a target adenosine. In some embodiments, the sugar of a second nucleoside does not contain any 2'-OR modifications as described herein (e.g., 2'-OMe, 2'-MOE etc.). In some embodiments, such a sugar is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, a third subdomain comprises one or more (e.g., 1-10, 1-5, 1-3, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars each independently comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2,-MOE, 2'-O−L^B−4' wherein L^B is optionally substituted

−CH_2−, etc.). In some embodiments, there are more such sugars in a third subdomain than 2'-F modified sugars.

[0009] In some embodiments, a second domain comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more modified sugars independently comprising a 2'-OR modification, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all sugars of a second domain comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl. In some embodiments, R is $-CH_2CH_2OCH_3$. As described herein, other sugar modifications may also be utilized in accordance with the present disclosure, optionally with base modifications and/or internucleotidic linkage modifications described herein.

[0010] In some embodiments, an oligonucleotide comprises or is of a 5'-first domain-second domain-3' structure. In some embodiments, a second domain comprises or is of a 5'-first subdomain-second subdomain-third subdomain-3' structure. In some embodiments, an oligonucleotide comprises or is of a 5'-first domain-first subdomain-second subdomain-third subdomain-3' structure. In some embodiments, oligonucleotide is conjugated to an additional moiety, e.g., various additional chemical moieties as described herein. In some embodiments, an oligonucleotide comprises an additional moiety, e.g., an additional moiety as described herein. In some embodiments, an additional chemical moiety is or comprises a small molecule moiety, a carbohydrate moiety (e.g., GalNAc moiety), a nucleic acid moiety (e.g., an oligonucleotide moiety, a nucleic acid moiety which can provide and/or modulate one or more properties and/or activities, etc. (e.g., a moiety of RNase H-dependent oligonucleotide, RNAi oligonucleotide, aptamer, gRNA, etc.), and/or a peptide moiety.

[0011] In some embodiments, base sequence of a provided oligonucleotide is substantially complementary to the base sequence of a target nucleic acid comprising a target adenosine. In some embodiments, a provided oligonucleotide when aligned to a target nucleic acid comprises one or more mismatches (non-Watson-Crick base pairs). In some embodiments, a provided oligonucleotide when aligned to a target nucleic acid comprises one or more wobbles (e.g., G-U, I-A, G-A, I-U, I-C, etc.). In some embodiments, mismatches and/or wobbles may help one or more proteins, e.g., ADAR1, ADAR2, etc., to recognize a duplex formed by a provided oligonucleotide and a target nucleic acid. In some embodiments, provided oligonucleotides form duplexes with target nucleic acids. In some embodiments, ADAR proteins recognize and bind to such duplexes. In some embodiments, nucleosides opposite to target adenosines are located in the middle of provided oligonucleotides, e.g., with 5-50 nucleosides to 5' side, and 1-50 nucleosides on its 3' side. In some embodiments, a 5' side has more nucleosides than a 3' side. In some embodiments, a 5' side has fewer nucleosides than a 3' side. In some embodiments, a 5' side has the same number of nucleosides as a 3' side. In some embodiments, provided oligonucleotides comprise 15-40, e.g., 15, 20, 25, 30, etc. contiguous bases of oligonucleotides described in the Tables. In some embodiments, base sequences of provided oligonucleotides are or comprises base sequences of oligonucleotides described in the Tables.

[0012] In some embodiments, with utilization of various structural elements (e.g., various modifications, stereochemistry, and patterns thereof), the present disclosure can achieve desired properties and high activities

with short oligonucleotides, e.g., those of about 20-40, 25-40, 25-35, 26-32, 25, 26, 27, 28, 29, 30, 31, 32 33, 34 or 35 nucleobases in length.

[0013] In some embodiments, provided oligonucleotides comprise modified nucleobases. In some embodiments, a modified nucleobase promotes modification of a target adenosine. In some embodiments, a nucleobase which is opposite to a target adenine maintains interactions with an enzyme, e.g., ADAR, compared to when a U is present, while interacts with a target adenine less strongly than U (e.g., forming fewer hydrogen bonds). In some embodiments, an opposite nucleobase and/or its associated sugar provide certain flexibility (e.g., when compared to U) to facility modification of a target adenosine by enzymes, e.g., ADAR1, ADAR2, etc. In some embodiments, a nucleobase immediately 5' or 3' to the opposite nucleobase (to a target adenine), e.g., I and derivatives thereof, enhances modification of a target adenine. Among other things, the present disclosure recognizes that such a nucleobase may causes less steric hindrance than G when a duplex of a provided oligonucleotide and its target nucleic acid interact with a modifying enzyme, e.g., ADAR1 or ADAR2. In some embodiments, base sequences of oligonucleotides are selected (e.g., when several adenosine residues are suitable targets) and/or designed (e.g., through utilization of various nucleobases described herein) so that steric hindrance may be reduced or removed (e.g., no G next to the opposite nucleoside of a target A).

[0014] In some embodiments, oligonucleotides of the present disclosure provides modified internucleotidic linkages (i.e., internucleotidic linkages that are not natural phosphate linkages). In some embodiments, linkage phosphorus of modified internucleotidic linkages (e.g., chiral internucleotidic linkages) are chiral and can exist in different configurations (*R*p and *S*p). Among other things, the present disclosure demonstrates that incorporation of modified internucleotidic linkage, particularly with control of stereochemistry of linkage phosphorus centers (so that at such a controlled center one configuration is enriched compared to stereorandom oligonucleotide preparation), can significantly improve properties (e.g., stability) and/or activities (e.g., adenosine modifying activities (e.g., converting an adenosine to inosine). In some embodiments, provided oligonucleotides have stereochemical purity significantly higher than stereorandom preparations. In some embodiments, provided oligonucleotides are chirally controlled.

[0015] In some embodiments, oligonucleotides of the present disclosure comprise one or more chiral internucleotidic linkages whose linkage phosphorus is chiral (e.g., a phosphorothioate internucleotidic linkage). In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% (e.g., 50%-100%, 60%-100%, 70-100%, 75%-100%, 80%-100%, 90%-100%, 95%-100%, 60%-95%, 70%-95%, 75-95%, 80-95%, 85-95%, 90-95%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, etc.) of all, or all internucleotidic linkages in an oligonucleotide, are chiral internucleotidic linkages. In some embodiments, at least one internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, at least one internucleotidic linkage is a natural phosphate linkage. In some embodiments, each internucleotidic linkage is independently a chiral internucleotidic linkage. In some embodiments, at least one chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each is a phosphorothioate internucleotidic

linkage. In some embodiments, one or more chiral internucleotidic linkages are independently a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, one or more chiral internucleotidic linkages are independently a phosphoryl guanidine internucleotidic linkage. In some embodiments, one or more chiral internucleotidic linkages are independently chirally controlled. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled. In some embodiments, one or more chiral internucleotidic linkages are not chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a phosphoryl guanidine internucleotidic linkage. In some embodiments, a phosphoryl guanidine internucleotidic linkage is n001. In some embodiments, each phosphoryl guanidine internucleotidic linkage is n001. In some embodiments, each non-negatively charged internucleotidic linkage is n001. In some embodiments, each neutral internucleotidic linkage is n001. In some embodiments, a modified internucleotidic linkage n002. In some embodiments, it is n006. In some embodiments, it is n020. In some embodiments, it is n004. In some embodiments, it is n008. In some embodiments, it is n025. In some embodiments, it is n026. Various modified internucleotidic linkages are described herein. A linkage phosphorus can be either *R*p or *S*p. In some embodiments, at least one linkage phosphorus is *R*p. In some embodiments, at least one linkage phosphorus is *S*p. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% (e.g., 50%-100%, 60%-100%, 70-100%, 75%-100%, 80%-100%, 90%-100%, 95%-100%, 60%-95%, 70%-95%, 75-95%, 80-95%, 85-95%, 90-95%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, etc.) of all, or all chiral internucleotidic linkages in an oligonucleotide, are *S*p. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% (e.g., 50%-100%, 60%-100%, 70-100%, 75%-100%, 80%-100%, 90%-100%, 95%-100%, 60%-95%, 70%-95%, 75-95%, 80-95%, 85-95%, 90-95%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, etc.) of all, or all phosphorothioate internucleotidic linkages in an oligonucleotide, are *S*p. In some embodiments, at least 50% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 60% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 70% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 75% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 80% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 85% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 90% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 95% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 96% of all phosphorothioate internucleotidic linkage are *S*p. In some

embodiments, at least 97% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, at least 98% of all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, all phosphorothioate internucleotidic linkage are *S*p. In some embodiments, no more than 3, 4, 5, 6, 7, 8, 9, or 10 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 3 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 4 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 5 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 6 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 7 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 8 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 9 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, no more than 10 consecutive phosphorothioate internucleotidic linkages are *R*p. In some embodiments, consecutive *R*p phosphorothioate internucleotidic linkages are not utilized in portions wherein the majority (e.g., greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) or all of sugars are natural DNA and/or RNA and/or 2'-F modified sugars. In some embodiments, when consecutive *R*p phosphorothioate internucleotidic linkages are utilized, one or more or the majority (e.g., greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) or all of such internucleotidic linkages are independently bonded to sugars which can improve stability. In some embodiments, when consecutive *R*p phosphorothioate internucleotidic linkages are utilized, one or more or the majority (e.g., greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) or all of such internucleotidic linkages are independently bonded to bicyclic sugars or 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, when consecutive *R*p phosphorothioate internucleotidic linkages are utilized, one or more or the majority (e.g., greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) or all of such internucleotidic linkages are independently bonded to 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar or a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE modified sugar.

[0016] In some embodiments, stereochemistry of one or more chiral linkage phosphorus of provided oligonucleotides are controlled in a composition. In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides, wherein oligonucleotides of a plurality share a common base sequence, and the same configuration of linkage phosphorus (e.g., all are *R*p or all are *S*p for the chiral linkage phosphorus) independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all chiral internucleotidic linkages) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages"). In some embodiments, they share the same stereochemistry at each chiral linkage phosphorus. In some

embodiments, oligonucleotides of a plurality share the same constitution. In some embodiments, oligonucleotides of a plurality are structurally identical except the internucleotidic linkages. In some embodiments, oligonucleotides of a plurality are structurally identical. In some embodiments, at least at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in a composition, or of all oligonucleotides sharing the common base sequence, share the pattern of backbone chiral centers of oligonucleotides of the plurality. In some embodiments, at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in a composition, or of all oligonucleotides sharing the common base sequence, are oligonucleotides of the plurality.

[0017] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition of an oligonucleotide, wherein at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in a composition, or of all oligonucleotides having the same base sequence of the oligonucleotide, or of all oligonucleotide having the same base sequence and sugar and base modifications, or of all oligonucleotides of the same constitution, share the same configuration of linkage phosphorus (e.g., all are *R*p or all are *S*p for the chiral linkage phosphorus) independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more, or at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all chiral internucleotidic linkages) chiral internucleotidic linkages with the oligonucleotide. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition of an oligonucleotide, wherein at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all oligonucleotides in a composition, or of all oligonucleotides having the same base sequence of the oligonucleotide, or of all oligonucleotide having the same base sequence and sugar and base modifications, or of all oligonucleotides of the same constitution, are one or more forms of the oligonucleotide (e.g., acid forms, salt forms (e.g. pharmaceutically acceptable salt forms; as appreciated by those skilled in the art, in case the oligonucleotide is a salt, other salt forms of the corresponding acid or base form of the oligonucleotide), etc.).

[0018] In some embodiments, as demonstrated herein chirally controlled oligonucleotide compositions provide a number of advantages, e.g., higher stability, activities, etc., compared to corresponding stereorandom oligonucleotide compositions. In some embodiments, it was observed that chirally controlled oligonucleotide compositions provide high levels of adenosine modifying (e.g., converting A to I) activities with various isoforms of an ADAR protein (e.g., p150 and p110 forms of ADAR1) while corresponding stereorandom compositions provide high levels of adenosine modifying (e.g., converting A to I) activities with only certain isoforms of an ADAR protein (e.g., p150 isoform of ADAR1).

[0019] In some embodiments, provided oligonucleotides comprise an additional moiety, e.g., a targeting moiety, a carbohydrate moiety, etc. In some embodiments, an additional moiety is or comprises a ligand for an asialoglycoprotein receptor. In some embodiments, an additional moiety is or comprises GalNAc or derivatives thereof. Among other things, additional moieties may facilitate delivery to certain target locations, e.g., cells, tissues, organs, etc. (e.g., locations comprising receptors that interact with additional moieties). In

some embodiments, additional moieties facilitate delivery to liver.

[0020] In some embodiments, the present disclosure provides technologies for preparing oligonucleotides and compositions thereof, particularly chirally controlled oligonucleotide compositions. In some embodiments, provided oligonucleotides and compositions thereof are of high purity. In some embodiments, oligonucleotides of the present disclosure are at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% stereochemically pure at linkage phosphorus of chiral internucleotidic linkages. In some embodiments, oligonucleotides of the present disclosure are prepared stereoselectively and are substantially free of stereoisomers. In some embodiments, in provided compositions comprising a plurality of oligonucleotides which share the same base sequence of the same pattern of chiral linkage phosphorus stereochemistry (e.g., comprising one or more of *R*p and/or *S*p, wherein each chiral linkage phosphorus is independently *R*p or *S*p), at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all oligonucleotides in the composition that share the same base sequence as oligonucleotides of the plurality share the same pattern of chiral linkage phosphorus stereochemistry or are oligonucleotides of the plurality. In some embodiments, in provided compositions comprising a plurality of oligonucleotides which share the same base sequence of the same pattern of chiral linkage phosphorus stereochemistry, at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of all oligonucleotides in the composition that share the same constitution as oligonucleotides of the plurality share the same pattern of chiral linkage phosphorus stereochemistry or are oligonucleotides of the plurality.

[0021] In some embodiments, the present disclosure describes useful technologies for assessing oligonucleotide and compositions thereof. For example, various technologies of the present disclosure are useful for assessing adenosine modification. As appreciated by those skilled in the art, in some embodiments, modification/editing of adenosine can be assessed through sequencing, mass spectrometry, assessment (e.g., levels, activities, etc.) of products (e.g., RNA, protein, etc.) of modified nucleic acids (e.g., wherein adenosines of target nucleic acids are converted to inosines), etc., optionally in view of other components (e.g., ADAR proteins) presence in modification systems (e.g., an *in vitro* system, an *ex vivo* system, cells, tissues, organs, organisms, subjects, etc.). Those skilled in the art will appreciate that oligonucleotides which provide adenosine modification of a target nucleic acid can also provide modified nucleic acid (e.g., wherein a target adenosine is converted into I) and one or more products thereof (e.g., mRNA, proteins, etc.). Certain useful technologies are described in the Examples.

[0022] As described herein, oligonucleotides and compositions of the present disclosure may be provided/utilized in various forms. In some embodiments, the present disclosure provides compositions comprising one or more forms of oligonucleotides, e.g., acid forms (e.g., in which natural phosphate linkages exist as –O(P(O)(OH)–O–, phosphorothioate internucleotidic linkages exist as –O(P(O)(SH)–O–), base forms, salt forms (e.g., in which natural phosphate linkages exist as salt forms (e.g., sodium salt (–O(P(O)(O^-Na^+)–O–), phosphorothioate internucleotidic linkages exist as salt forms (e.g., sodium salt (–O(P(O)(S^-Na^+)–O–) etc. As appreciated by those skilled in the art, oligonucleotides can exist in various salt

forms, including pharmaceutically acceptable salts, and in solutions (e.g., various aqueous buffering system), cations may dissociate from anions. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a provided oligonucleotide and/or one or more pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier. In some embodiments, pharmaceutical compositions are chirally controlled oligonucleotide compositions.

[0023] Provided technologies can be utilized for various purposes. For example, those skilled in the art will appreciate that provided technologies are useful for many purposes involving modification of adenosine, e.g., correction of G to A mutations, modulate levels of certain nucleic acids and/or products encoded thereby (e.g., reducing levels of proteins by introducing A to G/I modifications), modulation of splicing, modulation of translation (e.g., modulating translation start and/or stop site by introducing A to G/I modifications), etc.

[0024] In some embodiments, the present disclosure provides technologies for preventing or treating a condition, disorder or disease that is amenable to an adenosine modification, e.g. conversion of A to I or G. As appreciated by those skilled in the art, I may perform one or more functions of G, e.g., in base pairing, translation, etc. In some embodiments, a G to A mutation may be corrected through conversion of A to I so that one or more products, e.g., proteins, of the G-version nucleic acid can be produced. In some embodiments, the present disclosure provides technologies for preventing or treating a condition, disorder or disease associated with a mutation, comprising administering to a subject susceptible thereto or suffering therefrom a provided oligonucleotide or composition thereof, which oligonucleotide or composition can edit a mutation. In some embodiments, the present disclosure provides technologies for preventing or treating a condition, disorder or disease associated with a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom a provided oligonucleotide or composition thereof, which oligonucleotide or composition can modify an A. In some embodiments, provided technologies modify an A in a transcript, e.g., RNA transcript. In some embodiments, an A is converted into an I. In some embodiments, during translation protein synthesis machineries read I as G. In some embodiments, an A form encodes one or more proteins that have one or more higher desired activities and/or one or more better desired properties compared those encoded by its corresponding G form. In some embodiments, an A form provides higher levels, compared to its corresponding G form, of one or more proteins that have one or more higher desired activities and/or one or more better desired properties. In some embodiments, products encoded by an A form are structurally different (e.g., longer, in some embodiments, full length proteins) from those encoded by its corresponding G form. In some embodiments, an A form provides structurally identical products (e.g., proteins) compared to its corresponding G form.

[0025] As those skilled in the art will appreciate, many conditions, disorders or diseases are associated with mutations that can be modified by provided technologies and can be prevented and/or treated using provided technologies. For example, it is reported that there are over 20,000 conditions, disorders or diseases are associated with G to A mutation and can benefit from A to I editing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1. Provided technologies provide editing of mutations associated with conditions, disorders or diseases and provide products with improved properties and/or functions. Oligonucleotide compositions target a PiZ mutation of SERPINA1 (SA1). Primary mouse hepatocytes expressing the human SA1-PiZ allele were transfected with indicated oligonucleotide compositions (25 nM oligonucleotides) (WV-38621, WV-38622, WV-38630, and non-targeting (NT) control WV-37317). Media and RNA were collected 5 days post-transfection. RNA editing was quantified by RT-PCR and Sanger sequencing. A1AT protein in media was quantified by an ELISA assay ("SerpinA1 ng/ml"). All samples were assessed at N=6 replicates. As confirmed by data shown in the Figure, provided technologies can provide editing of target human SERPINA1-PIZ mRNA. Furthermore, data in the Figure confirm that provided technologies increase levels of A1AT protein secretion which indicates that provided technologies can correct mutations on protein levels and can provide proteins with improved correct folding of the A1AT protein (P-value: * <0.05, ** < 0.01, *** <0.005, and **** <0.0005).

[0027] Figure 2. Provided technologies can provide editing. (a) Certain oligonucleotides targeting a SERPINA1-Z allele. Indicated cell lines were stably infected with a lentivirus expressing a SERPINA1-Z allele transcript and transfected with the indicated oligonucleotide. HEK293T cells were also pre-transfected with a plasmid expressing ADAR1-p110 or ADAR1-p150. RNA was collected 48 hours later, and RNA editing was quantified by Sanger sequencing (n=2 biological replicates). (b) Oligonucleotides target a SERPINA1-Z allele. Indicated cell lines were stably infected with a lentivirus expressing the SERPINA1-Z allele transcript and transfected with the indicated oligonucleotide. HEK 293T cells were also pre-transfected with a plasmid expressing ADAR1-p110 or ADAR1-p150. RNA was collected 48 hours later, and RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0028] Figure 3. Provided technologies comprising various modifications, including modified bases, can provide editing. Oligonucleotides target a SERPINA1-Z allele. HEK293T or SF8628 cells stably expressing the SERPINA1-Z allele transcript were transfected indicated oligonucleotide. HEK293T cells were also pre-transfected with human ADAR1-p110 or p150. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0029] Figure 4. Provided technologies comprising various modifications, including modified bases, and various types of sugars can provide editing. Oligonucleotides target the SERPINA1-Z allele. HEK293T cells stably expressing the SERPINA1-Z allele transcript were transfected with human ADAR1-p110 or p150 and indicated oligonucleotide. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0030] Figure 5. Provided technologies comprising various modifications can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated GalNAc-conjugated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0031] Figure 6. Provided technologies can provide editing. Primary mouse hepatocytes were treated

with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0032] Figure 7. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0033] Figure 8. Provided technologies comprising various modifications, including base modifications, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele, were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0034] Figure 9. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0035] Figure 10. Provided technologies comprising various modifications, including modified internucleotide linkages, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0036] Figure 11. Provided technologies comprising various modifications, including modified internucleotide linkages, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting a SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0037] Figure 12. Provided technologies comprising various modifications, including sugar modifications, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0038] Figure 13. Provided technologies comprising various modifications, including sugar modifications, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0039] Figure 14. Provided technologies comprising oligonucleotides of various lengths can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0040] Figure 15. Provided technologies comprising various modifications, including various types of internucleotide linkages, can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 and SERPINA1-Z allele were treated with indicated oligonucleotides targeting SERPINA1-Z allele through

gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates)

[0041] Figure 16. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were treated with indicated GalNAc-conjugated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0042] Figure 17. Provided technologies comprising various types of sugars, nucleobases, internucleotidic linkages and/or additional chemical moieties can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were treated with indicated GalNAc-conjugated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0043] Figure 18. Provided technologies comprising various editing region base sequences can provide editing. (a) Oligonucleotides of various editing region sequences, including nearest neighbors adjacent to a nucleoside opposite to a target adenosine, were assessed. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotide targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates). (b) Oligonucleotides of various editing region sequences, including nearest neighbors adjacent to a nucleoside opposite to a target adenosine, were assessed. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates). (c) Oligonucleotides of various editing region sequences, including nearest neighbors adjacent to a nucleoside opposite to a target adenosine, were assessed. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0044] Figure 19. Provided technologies comprising various types of nucleosides and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0045] Figure 20. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0046] Figure 21. Provided technologies comprising various types of sugars, nucleosides, and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0047] Figure 22. Provided technologies comprising various types of sugars, nucleosides, and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA

editing was quantified by Sanger sequencing (n=2 biological replicates).

[0048] Figure 23. Provided technologies comprising various types of sugars, nucleosides, and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0049] Figure 24. Provided technologies comprising various types of sugars, nucleosides, and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0050] Figure 25. Provided technologies comprising various types of sugars, nucleosides, and internucleotidic linkages can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates).

[0051] Figure 26. Provided technologies can provide editing. Oligonucleotides comprising wobble base pairs, e.g., G-U wobble base pairs, at various positions can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were gymnotically treated with indicated oligonucleotides targeting SERPINA-Z.

[0052] Figure 27. Provided technologies comprising various modifications, including nucleoside modifications, can provide editing. Oligonucleotides target an adenosine in the 3'UTR of beta-actin mRNA. Primary human hepatocytes were gymnotically treated with indicated oligonucleotides at indicated concentrations. Editing of target was measured by Sanger sequencing (n=2 biological replicates).

[0053] Figure 28. Provided technologies comprising various modifications, including sugar modifications and modified internucleotidic linkages, can provide editing. Oligonucleotides target an adenosine in the 3'UTR of beta-actin mRNA. Primary human hepatocytes were gymnotically treated with indicated oligonucleotide at indicated concentrations. Editing of target was measured by Sanger sequencing (n=2 biological replicates).

[0054] Figure 29. Provided technologies can provide editing. Oligonucleotides target an adenosine in the 3'UTR of beta-actin mRNA. Primary human hepatocytes were gymnotically treated with indicated oligonucleotides at indicated concentrations. Editing of target was measured by Sanger sequencing (n=2 biological replicates).

[0055] Figure 30. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for human ADAR1-p110 were treated with indicated oligonucleotides targeting UGP2 through gymnotic uptake for 48 hrs. RNA editing was quantified by Sanger sequencing (n=2 biological replicates)

[0056] Figure 31. Provided technologies can provide editing in NHPs. (a) Non-human primates (NHPs) were dosed subcutaneously with indicated oligonucleotides (50 mg/kg, n=3 animals) or PBS (n=1 animal). 7 days later, animals were necropsied and indicated tissues were collected. RNA editing was quantified by

Sanger sequencing (n=2 biological replicates). (b): Corresponding concentration of oligonucleotides in indicated tissue, as measured by hybridization ELISA.

[0057] Figure 32. Provided technologies comprising various modifications can provide editing. (a) Non-human primates (NHPs) were dosed intrathecally with indicated oligonucleotides (5mg or 10mg, n=2 animals each) or artificial cerebrospinal fluid (aCSF) control (n=1 animal). Animals were necropsied on day 8 (aCSF, 5mg, 10mg groups) or day 29 (10mg group) and indicated tissues were collected. RNA editing was quantified by Sanger sequencing (n=2 biological replicates). (b): Corresponding concentration of oligonucleotides in indicated tissue, as measured by hybridization ELISA.

[0058] Figure 33. Provided technologies comprising duplexing designs can provide editing. Illustrated oligonucleotide compositions comprise two oligonucleotides that share a 16 or 18-bp complementary sequence, allowing them to associate and create double-stranded RNA structures that can recruit ADAR. One oligonucleotide (36 or 32-bp) also contains a targeting portion that is specifically complementary to a target of interest. As shown, combined oligonucleotide designs target a premature UAG stop codon within a cLuc coding sequence as an example. HEK293T cells were transfected with plasmids encoding human ADAR1-p150, luciferase reporter construct and indicated combination of oligonucleotides. cLuc activity was normalized to Gluc expression in mock treated samples. For each oligonucleotide comprising a duplex region and a target region (WV-42707 to WV-42710 and WV-42715 to WV-42718), duplexing oligonucleotides from the first to last are WV-42719 to WV-42730 (i.e., WV-42719, WV- 42720, WV- 42721, WV- 42722, WV-42723, WV- 42724, WV- 42725, WV- 42726, WV- 42727, WV- 42728, WV- 42729, and WV-42730).

[0059] Figure 34. Provided technologies comprising duplexing designs can provide editing. In some embodiments, a first oligonucleotide (e.g., a duplexing oligonucleotide) comprises a stem loop and can form duplex and a 2nd oligonucleotide (e.g., an oligonucleotide comprising a duplexing region and a targeting region) that can be used to target a specific transcript. In some embodiments, a first and a second oligonucleotides complementary sequence (e.g., of 15 nt) allowing them to associate. In some embodiments, formed duplexes recruit ADAR polypeptides such as ADAR1, ADAR2, etc. In Figure 34, combined oligonucleotide designs target a premature UAG stop codon within a cLuc coding sequence. HEK293T cells were transfected with plasmids encoding human ADAR1-p110 or p150, luciferase reporter construct and indicated combination of oligonucleotides. cLuc activity was normalized to Gluc expression in mock treated samples. As shown, various combinations provide editing activities.

[0060] Figure 35. Certain oligonucleotide designs as examples. (a) A duplexing oligonucleotide and an oligonucleotide comprising a duplexing region and a targeting region. (b) A duplexing oligonucleotide comprising a stem loop and an oligonucleotide comprising a duplexing region and a targeting region.

[0061] Figure 36. Various oligonucleotide compositions can provide editing. Primary mouse hepatocytes from transgenic model (expressing human ADARp110 and human SERPINA1-Z allele) were treated with indicated GalNAc-conjugated oligonucleotides targeting the SERPINA1-Z allele for 48 hrs. RNA editing was measured by Sanger sequencing.

[0062] Figure 37. Various oligonucleotide compositions can provide *in vivo* editing. A huADAR/SA1 transgenic mouse model was dosed 3x10mg/kg subcutaneously with the indicated oligonucleotides targeting the SERPINA1-Z allele. Mice were dosed every other day for 3 days (Days 0, 2, 4) and liver biopsies were collected on Day 7. Percent editing was measured by Sanger sequencing. One-way ANOVA with correction for multiple comparisons (Dunnett's) was used to test for differences SERPINA1-Z allele editing in treated vs. PBS groups. ****: P-value is less than 0.0001; ***: P-value is less than 0.001; **: P-value is less than 0.005. P-values were calculated from comparison of pre-dose and Day 7 values for each sample.

[0063] Figure 38. Various oligonucleotide compositions can increase serum AAT following *in vivo* editing. Serum was collected from mice prior to dosing and on Day 7 following treatment as described for Figure 37. Concentration of total human AAT in serum was determined by a commercially available ELISA kit (AbCam). Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS. ****: P-value is less than 0.0001; ***: P-value is less than 0.001; **: P-value is less than 0.005. P-values were calculated from comparison of pre-dose and Day 7 values for each sample.

[0064] Figure 39. Provided oligonucleotide composition can decrease mutant Z-AAT protein level and increase wild-type AAT protein level in serum. Serum was collected from mice prior to dosing and on Day 7 following treatment as described for Figure 37. Relative abundance of Z (mutant) vs. M (wild-type) AAT isoforms was determined by mass spectrometry. Absolute amounts of each isoform were then calculated by applying relative abundances to absolute concentrations obtained from ELISA (see Figure 38).

[0065] Figure 40. Editing by various oligonucleotide compositions can result in functional wild-type AAT protein. Serum was collected from mice prior to dosing and on Day 7 following treatment as described for Figure 37. Relative elastase inhibition activity in serum was determined using a commercially available kit (EnzChek® Elastase Assay Kit (E-12056)). Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in elastase inhibition activity in serum collected at day 7 vs pre-dose for each treatment group. ****: P-value is less than 0.0001; ***: P-value is less than 0.001; **: P-value is less than 0.005. P-values were calculated from comparison of pre-dose and Day 7 values for each sample.

[0066] Figure 41. Provided technologies can modulate protein-protein interactions. (a) Provided oligonucleotide compositions edit adenosines in Keap1 and NRF2 transcripts. HEK293T cells were transfected with oligonucleotide compositions targeting Keap1 or NRF2 and a plasmid expressing either ADAR-p110 (upper bars) or ADAR1-p150 (lower bars). RNA was collected 48 hours after treatment and RNA editing of Keap1 and NRF2 transcripts was measured by Sanger sequencing. "*": data not available. (b) Provided oligonucleotide technologies can modulate gene expression. HEK293T cells were transfected with indicated oligonucleotides targeting NRF2 or Keap1 and a plasmid expressing either ADAR-p110 or ADAR1-p150. RNA was collected 48 hours after treatment. Fold change in various genes regulated by NRF2 was measured by qPCR.

[0067] Figure 42. Provided technologies can provide robust and durable editing *in vivo*. hADAR mice were treated with a single 100 ug ICV injection of oligonucleotide composition comprising WV-40590 oligonucleotides targeting UGP2. UGP2 editing was measured between 1-16 weeks post-dosage.

[0068] Figure 43. Provided technologies can provide editing. Primary human hepatocytes were treated with oligonucleotide compositions targeting UGP2 at 1uM (left bar) and 0.3 uM (right bar) via gymnotic uptake. RNA was collected 48 hours post-treatment and RNA editing was measured by Sanger sequencing (n=2 biological replicates).

[0069] Figure 44. Provided technologies can provide editing. Human IPSC derived neurons (iCells) were treated with oligonucleotide compositions comprising indicated oligonucleotides targeting UGP2 at 3 uM (left bar) and 1 uM (right bar) via gymnotic uptake. RNA was collected 6 days post-treatment and RNA editing was measured by Sanger sequencing (n=2 biological replicates).

[0070] Figure 45. Provided technologies can provide editing *in vivo*. Wild-type (Wt) and hADAR mice were treated with PBS (left bar) or oligonucleotide compositions (middle bar = WV-38702, right bar = WV-48161) targeting UGP2 via three sub-cutaneous doses of 10 mg/kg (days 0, 2, and 4, respectively). Mouse livers were isolated 1 week post-treatment and RNA was collected. RNA editing was measured by Sanger sequencing (n=2 biological replicates).

[0071] Figure 46. Provided technologies can provide editing in various cell populations including immune cells. Human PBMCs were treated with oligonucleotide compositions targeting ACTB at 10 uM concentration under activating (addition of PHA) or non-activating (no addition of PHA) conditions (left bar = mock, middle bar = WV-37317 with PHA, right bar = WV=37317 without PHA). Cells were treated via gymnotic uptake. Cells were isolated 4 days post-treatment using benchtop antibody/bead protocols. RNA was collected and RNA editing was measured by Sanger sequencing (n=2 biological replicates).

[0072] Figure 47. Provided technologies can provide editing *in vivo* including in eyes. hADAR mice were treated with oligonucleotide compositions targeting UGP2 at indicated dosages via intracerebroventricular (ICV) injection in posterior compartment of eyes. Mouse eyes were isolated at 1 and 4 week(s) post-treatment and RNA was isolated. RNA editing was measured by PCR and Sanger sequencing.

[0073] Figure 48. Provided technologies can provide durable editing *in vivo*. Mice transgenic for hADAR and SERPINA1-Z allele were treated with oligonucleotide compositions targeting SERPINA1-Z allele at 10 mg/kg doses on days 0, 2, and 4 via subcutaneous administration. Mouse serum was collected through weekly blood draws on indicated days post-treatment. (a) Levels of human AAT protein were measured by ELISA. . Data are presented as mean ± sem. Stats: Matched 2-way ANOVA; ns: non-significant, **: $P<0.01$, ***: $P<0.001$. (b) Mass spectrometry and ELISA were used to determine relative proportions of wild-type (WT / M-AAT) and mutant (Z-AAT / Mutant) AAT protein.

[0074] Figure 49. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for hADARp110 and SERPINA1-Z allele were treated with oligonucleotide compositions comprising indicated GalNAc-conjugated oligonucleotides targeting SERPINA1-Z allele at indicated concentrations. RNA was

isolated 48 hours post-treatment and RNA editing was measured by Sanger sequencing (n=2 biological replicates).

[0075] Figure 50. Provided technologies can provide editing *in vivo*. Mice transgenic for hADAR and SERPINA1-Z allele were treated with oligonucleotide compositions targeting SERPINA1-Z allele at 5 mg/kg doses on days 0, 2, and 4 via subcutaneous administration. Mouse liver biopsies were collected on day 7 post-treatment. RNA editing was measured by Sanger sequencing in male (left bar) and female (right bar) mice (n=3 animals per gender).

[0076] Figure 51. Provided technologies can provide editing. Primary mouse hepatocytes transgenic for hADARp110 and SERPINA1-Z allele were treated with oligonucleotide compositions targeting SERPINA-Z allele at indicated concentrations. RNA was isolated 48 hours post-treatment and RNA editing was measured by Sanger sequencing (n=3 biological replicates).

[0077] Figure 52. Provided technologies can provide functional edited polypeptides *in vivo*. Mice transgenic for hADAR and SERPINA1-Z allele were treated with oligonucleotide compositions targeting SERPINA1-Z allele at 10 mg/kg doses on days 0, 2, and 4 via subcutaneous administration. Mouse serum was collected through weekly blood draws on indicated days. Levels of human AAT protein was quantified by ELISA and mass spectrometry to assess relative proportions of wild-type (PiM / WT, left bar) and mutant (PiZ / Mutant, right bar) AAT protein.

[0078] Figure 53. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0079] Figure 54. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0080] Figure 55. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates)

[0081] Figure 56. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b001A, b008U, b010U, b001C, b008C, b011U, b002G, b012U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for

humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[0082] Figure 57. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, b010U, b001C, b008C, b011U, b012U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[0083] Figure 58. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as nucleobase modifications, linkage modifications, sugar modifications, etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[0084] Figure 59. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, e.g., Csm11, Csm12, b009Csm11, b009Csm12, Gsm11, Gsm12, Tsm11, Tsm12, L010, etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[0085] Figure 60. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, sm15, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0086] Figure 61. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, b001A, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0087] Figure 62. Provided technologies can provide editing. Among other things, it is shown that 2'-OR modifications wherein R is not −H can be utilized at various positions. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0088] Figure 63. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g.,

PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0089] Figure 64. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0090] Figure 65. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0091] Figure 66. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0092] Figure 67. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0093] Figure 68. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0094] Figure 69. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g.,

PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0095] Figure 70. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0096] Figure 71. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, sm15, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0097] Figure 72. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, e.g., linkages such as n001, n002, n006, n020, etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[0098] Figure 73. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b001A, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, morpholine sugars, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[0099] Figure 74. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b001A, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, morpholine sugars, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[00100] Figure 75. Various nearest neighbors can provide editing activity. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[00101] Figure 76. Provided technologies can provide editing. Compositions of oligonucleotides

comprising various modifications (*e.g.*, b008U, b012U, b013U, b001A, b002A, b003A, b004I, b002G, b009U, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[00102] Figure 77. Provided technologies can provide editing. Compositions of oligonucleotides comprising various sugar and nucleobase modifications (*e.g.*, in b002A, b003A, b008U, b001C, Tsm11, Tsm12, b004C, b007C, 2'-F, 2'-OMe, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[00103] Figure 78. Provided technologies can provide editing. Compositions of oligonucleotides comprising various sugar and nucleobase modifications (*e.g.*, in b003A, b008U, b001C, b008C, Tsm11, Tsm12, b004C, Csm17, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates).

[00104] Figure 79. Provided technologies can provide editing. Compositions of oligonucleotides comprising various sugars and nucleobases (*e.g.*, in dI, b001A, b003A, b008U, b001C, b008C, Tsm11, Tsm12, b004C, Csm17, etc. at N_{-1}), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[00105] Figure 80. Provided technologies can provide editing. Compositions of oligonucleotides comprising various sugars and nucleobases (*e.g.*, in dI, b001A, b002A, b003A, b008U, b008C, Tsm11, Tsm12, b004C, Csm17, etc. at N_{-1}), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[00106] Figure 81. Provided technologies can provide editing. Compositions of oligonucleotides comprising various sugars and nucleobases (*e.g.*, in Csm11, Csm12, b009Csm11, b009Csm12, etc. at N_{-1}), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates) for various oligonucleotide compositions.

[00107] Figure 82. Oligonucleotides comprising various types of internucleotidic linkages can provide

editing. Compositions of oligonucleotides comprising various modifications, such as base modifications (*e.g.*, b008U, b014I, etc.), linkage modifications (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001, n004, n008, n025, n026, etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., were prepared and assessed. Editing of target adenosines in SERPINA1-Z allele in primary mouse hepatocytes transgenic for humanADARp110 and SERPINA1-Z allele was confirmed (N=2 biological replicates). For each oligonucleotide composition, from left to right, 1.0, 0.33, 0.11, 0.037 uM, respectively.

[00108] Figure 83. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications and patterns thereof were prepared and assessed. Editing of target adenosines in UGP2 in primary human hepatocytes was confirmed (N=2 biological replicates) for various oligonucleotide compositions. Concentrations tested were 1 uM, 0.1 uM, and 0.01 uM, from left to right.

[00109] Figure 84. Provided technologies can provide editing. Compositions of oligonucleotides comprising various modifications and patterns thereof were prepared and assessed, and editing of target adenosines in UGP2 in primary human hepatocytes was confirmed at various concentrations.

[00110] Figure 85. Provided technologies can provide editing *in vivo*. *In vivo* editing of target adenosines in SERPINA1-Z allele in mice transgenic for human ADAR and SERPINA1-Z allele was confirmed. Serum levels of AAT in treated mice were also increased.

[00111] Figure 86. Provided technologies can provide editing *in vivo*. Oligonucleotides comprising various nucleobases (*e.g.*, b008U, hypoxanthine, etc.), linkages (e.g., PO, PS, PN (e.g., phosphoryl guanidine linkages such as n001), etc.), sugar modifications (e.g., 2'-F, 2'-OMe, 2'-MOE, etc.), etc., and patterns thereof were prepared. Editing of target adenosines and increase of serum AAT was confirmed (N=4 animals per group). Top: SERPINA1 editing at day 10. Bottom: serum AAT fold change.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[00112] Technologies of the present disclosure may be understood more readily by reference to the following detailed description of certain embodiments.

Definitions

[00113] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[00114] As used herein in the present disclosure, unless otherwise clear from context, (i) the term "a" or "an" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising", "comprise", "including" (whether used with "not limited to" or not), and "include" (whether used with "not limited to" or not) may be understood to encompass itemized components or steps

whether presented by themselves or together with one or more additional components or steps; (iv) the term "another" may be understood to mean at least an additional/second one or more; (v) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (vi) where ranges are provided, endpoints are included.

[00115] Unless otherwise specified, description of oligonucleotides and elements thereof (e.g., base sequence, sugar modifications, internucleotidic linkages, linkage phosphorus stereochemistry, patterns thereof, etc.) is from 5' to 3'. As those skilled in the art will appreciate, in some embodiments, oligonucleotides may be provided and/or utilized as salt forms, particularly pharmaceutically acceptable salt forms, e.g., sodium salts. As those skilled in the art will also appreciate, in some embodiments, individual oligonucleotides within a composition may be considered to be of the same constitution and/or structure even though, within such composition (e.g., a liquid composition), particular such oligonucleotides might be in different salt form(s) (and may be dissolved and the oligonucleotide chain may exist as an anion form when, e.g., in a liquid composition) at a particular moment in time. For example, those skilled in the art will appreciate that, at a given pH, individual internucleotidic linkages along an oligonucleotide chain may be in an acid (H) form, or in one of a plurality of possible salt forms (e.g., a sodium salt, or a salt of a different cation, depending on which ions might be present in the preparation or composition), and will understand that, so long as their acid forms (e.g., replacing all cations, if any, with H^+) are of the same constitution and/or structure, such individual oligonucleotides may properly be considered to be of the same constitution and/or structure.

[00116] Aliphatic: As used herein, "aliphatic" means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation (but not aromatic), or a substituted or unsubstituted monocyclic, bicyclic, or polycyclic hydrocarbon ring that is completely saturated or that contains one or more units of unsaturation (but not aromatic), or combinations thereof. In some embodiments, aliphatic groups contain 1-50 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-20 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-9 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-7 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1, 2, 3, or 4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[00117] Alkenyl: As used herein, the term "alkenyl" refers to an aliphatic group, as defined herein, having one or more double bonds.

[00118] Alkyl: As used herein, the term "alkyl" is given its ordinary meaning in the art and may include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some

embodiments, alkyl has 1-100 carbon atoms. In certain embodiments, a straight chain or branched chain alkyl has about 1-20 carbon atoms in its backbone (e.g., C_1-C_{20} for straight chain, C_2-C_{20} for branched chain), and alternatively, about 1-10. In some embodiments, cycloalkyl rings have from about 3-10 carbon atoms in their ring structure where such rings are monocyclic, bicyclic, or polycyclic, and alternatively about 5, 6 or 7 carbons in the ring structure. In some embodiments, an alkyl group may be a lower alkyl group, wherein a lower alkyl group comprises 1-4 carbon atoms (e.g., C_1-C_4 for straight chain lower alkyls).

[00119] Alkynyl: As used herein, the term "alkynyl" refers to an aliphatic group, as defined herein, having one or more triple bonds.

[00120] Analog: The term "analog" includes any chemical moiety which differs structurally from a reference chemical moiety or class of moieties, but which is capable of performing at least one function of such a reference chemical moiety or class of moieties. As non-limiting examples, a nucleotide analog differs structurally from a nucleotide but performs at least one function of a nucleotide; a nucleobase analog differs structurally from a nucleobase but performs at least one function of a nucleobase; etc.

[00121] Animal: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish and/or worms. In some embodiments, an animal may be a transgenic animal, a genetically-engineered animal and/or a clone.

[00122] Aryl: The term "aryl", as used herein, used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic, bicyclic or polycyclic ring systems having a total of five to thirty ring members, wherein at least one ring in the system is aromatic. In some embodiments, an aryl group is a monocyclic, bicyclic or polycyclic ring system having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, and wherein each ring in the system contains 3 to 7 ring members. In some embodiments, each monocyclic ring unit is aromatic. In some embodiments, an aryl group is a biaryl group. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, biphenyl, naphthyl, binaphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[00123] Characteristic portion: As used herein, the term "characteristic portion", in the broadest sense, refers to a portion of a substance whose presence (or absence) correlates with presence (or absence) of a particular feature, attribute, or activity of the substance. In some embodiments, a characteristic portion of a substance is a portion that is found in the substance and in related substances that share the particular feature,

attribute or activity, but not in those that do not share the particular feature, attribute or activity. In certain embodiments, a characteristic portion shares at least one functional characteristic with the intact substance. For example, in some embodiments, a "characteristic portion" of a protein or polypeptide is one that contains a continuous stretch of amino acids, or a collection of continuous stretches of amino acids, that together are characteristic of a protein or polypeptide. In some embodiments, each such continuous stretch generally contains at least 2, 5, 10, 15, 20, 50, or more amino acids. In general, a characteristic portion of a substance (*e.g.*, of a protein, antibody, *etc.*) is one that, in addition to the sequence and/or structural identity specified above, shares at least one functional characteristic with the relevant intact substance. In some embodiments, a characteristic portion may be biologically active.

[00124] Chiral control: As used herein, "chiral control" refers to control of the stereochemical designation of the chiral linkage phosphorus in a chiral internucleotidic linkage within an oligonucleotide. As used herein, a chiral internucleotidic linkage is an internucleotidic linkage whose linkage phosphorus is chiral. In some embodiments, a control is achieved through a chiral element that is absent from the sugar and base moieties of an oligonucleotide, for example, in some embodiments, a control is achieved through use of one or more chiral auxiliaries during oligonucleotide preparation, which chiral auxiliaries often are part of chiral phosphoramidites used during oligonucleotide preparation. In contrast to chiral control, a person having ordinary skill in the art will appreciate that conventional oligonucleotide synthesis which does not use chiral auxiliaries cannot control stereochemistry at a chiral internucleotidic linkage if such conventional oligonucleotide synthesis is used to form the chiral internucleotidic linkage. In some embodiments, the stereochemical designation of each chiral linkage phosphorus in each chiral internucleotidic linkage within an oligonucleotide is controlled.

[00125] Chirally controlled oligonucleotide composition: The terms "chirally controlled oligonucleotide composition", "chirally controlled nucleic acid composition", and the like, as used herein, refers to a composition that comprises a plurality of oligonucleotides (or nucleic acids) which share a common base sequence, wherein the plurality of oligonucleotides (or nucleic acids) share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled or stereodefined internucleotidic linkages, whose chiral linkage phosphorus is Rp or Sp in the composition ("stereodefined"), not a random Rp and Sp mixture as non-chirally controlled internucleotidic linkages). In some embodiments, a chirally controlled oligonucleotide composition comprises a plurality of oligonucleotides (or nucleic acids) that share: 1) a common base sequence, 2) a common pattern of backbone linkages, and 3) a common pattern of backbone phosphorus modifications, wherein the plurality of oligonucleotides (or nucleic acids) share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled or stereodefined internucleotidic linkages, whose chiral linkage phosphorus is Rp or Sp in the composition ("stereodefined"), not a random Rp and Sp mixture as non-chirally controlled internucleotidic linkages). Level of the plurality of oligonucleotides (or nucleic acids) in a chirally controlled oligonucleotide composition is pre-determined/controlled or enriched (e.g., through chirally controlled oligonucleotide preparation to

stereoselectively form one or more chiral internucleotidic linkages) compared to a random level in a non-chirally controlled oligonucleotide composition. In some embodiments, about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition are oligonucleotides of the plurality. In some embodiments, about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition that share the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone phosphorus modifications are oligonucleotides of the plurality. In some embodiments, a level is about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a composition, or of all oligonucleotides in a composition that share a common base sequence (e.g., of a plurality of oligonucleotide or an oligonucleotide type), or of all oligonucleotides in a composition that share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone phosphorus modifications, or of all oligonucleotides in a composition that share a common base sequence, a common patter of base modifications, a common pattern of sugar modifications, a common pattern of internucleotidic linkage types, and/or a common pattern of internucleotidic linkage modifications. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 1-50 (e.g., about 1-10, 1-20, 5-10, 5-20, 10-15, 10-20, 10-25, 10-30, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) chiral internucleotidic linkages. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 1%-100% (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%) of chiral internucleotidic linkages. In some embodiments, oligonucleotides (or nucleic acids) of a plurality share the same pattern of sugar and/or nucleobase modifications, in any. In some embodiments, oligonucleotides (or nucleic acids) of a plurality are various forms of the same oligonucleotide (e.g., acid and/or various salts of the same oligonucleotide). In some embodiments, oligonucleotides (or nucleic acids) of a plurality are of the same constitution. In some

embodiments, level of the oligonucleotides (or nucleic acids) of the plurality is about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides (or nucleic acids) in a composition that share the same constitution as the oligonucleotides (or nucleic acids) of the plurality. In some embodiments, each chiral internucleotidic linkage is a chiral controlled internucleotidic linkage, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, oligonucleotides (or nucleic acids) of a plurality are structurally identical. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%, typically at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 95%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 96%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 97%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 98%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 99%. In some embodiments, a percentage of a level is or is at least $(DS)^{nc}$, wherein DS is a diastereopurity as described in the present disclosure (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages as described in the present disclosure (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more). In some embodiments, a percentage of a level is or is at least $(DS)^{nc}$, wherein DS is 95%-100%. For example, when DS is 99% and nc is 10, the percentage is or is at least 90% ($(99\%)^{10} \approx 0.90 = 90\%$). In some embodiments, level of a plurality of oligonucleotides in a composition is represented as the product of the diastereopurity of each chirally controlled internucleotidic linkage in the oligonucleotides. In some embodiments, diastereopurity of an internucleotidic linkage connecting two nucleosides in an oligonucleotide (or nucleic acid) is represented by the diastereopurity of an internucleotidic linkage of a dimer connecting the same two nucleosides, wherein the dimer is prepared using comparable conditions, in some instances, identical synthetic cycle conditions (e.g., for the linkage between Nx and Ny in an oligonucleotide ….NxNy….., the dimer is NxNy). In some embodiments, not all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition. In some embodiments, a non-chirally controlled internucleotidic linkage has a diastereopurity of less than about 80%, 75%, 70%, 65%, 60%, 55%, or of about 50%, as typically observed in stereorandom oligonucleotide compositions (e.g., as appreciated by those skilled in the art, from traditional oligonucleotide synthesis, e.g., the phosphoramidite method). In some embodiments, oligonucleotides (or nucleic acids) of a plurality are of the same type. In some embodiments, a chirally controlled oligonucleotide composition comprises non-random or controlled

levels of individual oligonucleotide or nucleic acids types. For instance, in some embodiments a chirally controlled oligonucleotide composition comprises one and no more than one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises more than one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises multiple oligonucleotide types. In some embodiments, a chirally controlled oligonucleotide composition is a composition of oligonucleotides of an oligonucleotide type, which composition comprises a non-random or controlled level of a plurality of oligonucleotides of the oligonucleotide type.

[00126] Comparable: The term "comparable" is used herein to describe two (or more) sets of conditions or circumstances that are sufficiently similar to one another to permit comparison of results obtained or phenomena observed. In some embodiments, comparable sets of conditions or circumstances are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will appreciate that sets of conditions are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under the different sets of conditions or circumstances are caused by or indicative of the variation in those features that are varied.

[00127] Cycloaliphatic: The term "cycloaliphatic," "carbocycle," "carbocyclyl," "carbocyclic radical," and "carbocyclic ring," are used interchangeably, and as used herein, refer to saturated or partially unsaturated, but non-aromatic, cyclic aliphatic monocyclic, bicyclic, or polycyclic ring systems, as described herein, having, unless otherwise specified, from 3 to 30 ring members. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, adamantyl, and cyclooctadienyl. In some embodiments, a cycloaliphatic group has 3–6 carbons. In some embodiments, a cycloaliphatic group is saturated and is cycloalkyl. The term "cycloaliphatic" may also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or tetrahydronaphthyl. In some embodiments, a cycloaliphatic group is bicyclic. In some embodiments, a cycloaliphatic group is tricyclic. In some embodiments, a cycloaliphatic group is polycyclic. In some embodiments, "cycloaliphatic" refers to C_3-C_6 monocyclic hydrocarbon, or C_8-C_{10} bicyclic or polycyclic hydrocarbon, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule, or a C_9-C_{16} polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule.

[00128] Heteroaliphatic: The term "heteroaliphatic", as used herein, is given its ordinary meaning in the art and refers to aliphatic groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (e.g., oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). In some embodiments, one or more units selected from C, CH, CH_2, and CH_3 are independently replaced by one or more heteroatoms (including oxidized and/or substituted forms thereof). In some embodiments, a heteroaliphatic group is heteroalkyl. In some embodiments, a heteroaliphatic group is heteroalkenyl.

[00129] Heteroalkyl: The term "heteroalkyl", as used herein, is given its ordinary meaning in the art and refers to alkyl groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (e.g., oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). Examples of heteroalkyl groups include, but are not limited to, alkoxy, poly(ethylene glycol)-, alkyl-substituted amino, tetrahydrofuranyl, piperidinyl, morpholinyl, etc.

[00130] Heteroaryl: The terms "heteroaryl" and "heteroar–", as used herein, used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to monocyclic, bicyclic or polycyclic ring systems having a total of five to thirty ring members, wherein at least one ring in the system is aromatic and at least one aromatic ring atom is a heteroatom. In some embodiments, a heteroaryl group is a group having 5 to 10 ring atoms (i.e., monocyclic, bicyclic or polycyclic), in some embodiments 5, 6, 9, or 10 ring atoms. In some embodiments, each monocyclic ring unit is aromatic. In some embodiments, a heteroaryl group has 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. In some embodiments, a heteroaryl is a heterobiaryl group, such as bipyridyl and the like. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Non-limiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be monocyclic, bicyclic or polycyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl group, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[00131] Heteroatom: The term "heteroatom", as used herein, means an atom that is not carbon or hydrogen. In some embodiments, a heteroatom is boron, oxygen, sulfur, nitrogen, phosphorus, or silicon (including oxidized forms of nitrogen, sulfur, phosphorus, or silicon; charged forms of nitrogen (e.g., quaternized forms, forms as in iminium groups, etc.), phosphorus, sulfur, oxygen; etc.). In some embodiments, a heteroatom is silicon, phosphorus, oxygen, sulfur or nitrogen. In some embodiments, a heteroatom is silicon, oxygen, sulfur or nitrogen. In some embodiments, a heteroatom is oxygen, sulfur or nitrogen.

[00132] Heterocycle: As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring", as used herein, are used interchangeably and refer to a monocyclic, bicyclic or polycyclic ring moiety (e.g., 3-30 membered) that is saturated or partially unsaturated and has one or more heteroatom ring atoms. In some embodiments, a heterocyclyl group is a stable 5– to 7–membered monocyclic or 7– to 10–

membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur and nitrogen, the nitrogen may be N (as in 3,4–dihydro–2H–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in N–substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3H–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be monocyclic, bicyclic or polycyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[00133] Identity: As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, e.g., between nucleic acid molecules (e.g., oligonucleotides, DNA, RNA, etc.) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “substantially identical” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or substantially 100% of the length of a reference sequence. The nucleotides at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (e.g., nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4: 11-17), which has been incorporated into the ALIGN program (version 2.0). In some exemplary embodiments, nucleic acid sequence comparisons made with the ALIGN program use a PAM120 weight residue table, a gap length penalty of 12 and a gap

penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix.

[00134] Internucleotidic linkage: As used herein, the phrase "internucleotidic linkage" refers generally to a linkage linking nucleoside units of an oligonucleotide or a nucleic acid. In some embodiments, an internucleotidic linkage is a phosphodiester linkage, as extensively found in naturally occurring DNA and RNA molecules (natural phosphate linkage (−OP(=O)(OH)O−), which as appreciated by those skilled in the art may exist as a salt form). In some embodiments, an internucleotidic linkage is a modified internucleotidic linkage (not a natural phosphate linkage). In some embodiments, an internucleotidic linkage is a "modified internucleotidic linkage" wherein at least one oxygen atom or −OH of a phosphodiester linkage is replaced by a different organic or inorganic moiety. In some embodiments, such an organic or inorganic moiety is selected from =S, =Se, =NR', –SR', –SeR', –N(R')$_2$, B(R')$_3$, –S–, –Se–, and –N(R')–, wherein each R' is independently as defined and described in the present disclosure. In some embodiments, an internucleotidic linkage is a phosphotriester linkage, phosphorothioate linkage (or phosphorothioate diester linkage, −OP(=O)(SH)O−, which as appreciated by those skilled in the art may exist as a salt form), or phosphorothioate triester linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate linkage. In some embodiments, an internucleotidic linkage is one of, e.g., PNA (peptide nucleic acid) or PMO (phosphorodiamidate Morpholino oligomer) linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage (e.g., n001 in certain provided oligonucleotides). It is understood by a person of ordinary skill in the art that an internucleotidic linkage may exist as an anion or cation at a given pH due to the existence of acid or base moieties in the linkage. In some embodiments, a modified internucleotidic linkages is a modified internucleotidic linkages designated as s, s1, s2, s3, s4, s5, s6, s7, s8, s9, s10, s11, s12, s13, s14, s15, s16, s17 and s18 as described in WO 2017/210647.

[00135] In vitro: As used herein, the term "in vitro" refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, etc., rather than within an organism (e.g., animal, plant and/or microbe).

[00136] In vivo: As used herein, the term "in vivo" refers to events that occur within an organism (e.g., animal, plant and/or microbe).

[00137] Linkage phosphorus: as defined herein, the phrase "linkage phosphorus" is used to indicate that the particular phosphorus atom being referred to is the phosphorus atom present in the internucleotidic linkage, which phosphorus atom corresponds to the phosphorus atom of a phosphodiester internucleotidic linkage as occurs in naturally occurring DNA and RNA. In some embodiments, a linkage phosphorus atom is in a modified internucleotidic linkage, wherein each oxygen atom of a phosphodiester linkage is optionally and independently replaced by an organic or inorganic moiety. In some embodiments, a linkage phosphorus atom is chiral (e.g., as in phosphorothioate internucleotidic linkages). In some embodiments, a linkage phosphorus atom is achiral (e.g., as in natural phosphate linkages).

[00138] Modified nucleobase: The terms "modified nucleobase", "modified base" and the like refer to a chemical moiety which is chemically distinct from a nucleobase, but which is capable of performing at least one function of a nucleobase. In some embodiments, a modified nucleobase is a nucleobase which comprises a modification. In some embodiments, a modified nucleobase is capable of at least one function of a nucleobase, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases. In some embodiments, a modified nucleobase is substituted A, T, C, G, or U, or a substituted tautomer of A, T, C, G, or U. In some embodiments, a modified nucleobase in the context of oligonucleotides refer to a nucleobase that is not A, T, C, G or U.

[00139] Modified nucleoside: The term "modified nucleoside" refers to a moiety derived from or chemically similar to a natural nucleoside, but which comprises a chemical modification which differentiates it from a natural nucleoside. Non-limiting examples of modified nucleosides include those which comprise a modification at the base and/or the sugar. Non-limiting examples of modified nucleosides include those with a 2' modification at a sugar. Non-limiting examples of modified nucleosides also include abasic nucleosides (which lack a nucleobase). In some embodiments, a modified nucleoside is capable of at least one function of a nucleoside, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

[00140] Modified nucleotide: The term "modified nucleotide" includes any chemical moiety which differs structurally from a natural nucleotide but is capable of performing at least one function of a natural nucleotide. In some embodiments, a modified nucleotide comprises a modification at a sugar, base and/or internucleotidic linkage. In some embodiments, a modified nucleotide comprises a modified sugar, modified nucleobase and/or modified internucleotidic linkage. In some embodiments, a modified nucleotide is capable of at least one function of a nucleotide, e.g., forming a subunit in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

[00141] *Modified sugar*: The term "modified sugar" refers to a moiety that can replace a sugar. A modified sugar mimics the spatial arrangement, electronic properties, or some other physicochemical property of a sugar. In some embodiments, as described in the present disclosure, a modified sugar is substituted ribose or deoxyribose. In some embodiments, a modified sugar comprises a 2'-modification. Examples of useful 2'-modification are widely utilized in the art and described herein. In some embodiments, a 2'-modification is 2'-F. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-10} aliphatic. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a modified sugar is a bicyclic sugar (e.g., a sugar used in LNA, BNA, etc.). In some embodiments, in the context of oligonucleotides, a modified sugar is a sugar that is not ribose or deoxyribose as typically found in natural RNA or DNA.

[00142] Nucleic acid: The term "nucleic acid", as used herein, includes any nucleotides and polymers thereof. The term "polynucleotide", as used herein, refers to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) or a combination thereof. These terms refer to

the primary structure of the molecules and, thus, include double- and single-stranded DNA, and double- and single-stranded RNA. These terms include, as equivalents, analogs of either RNA or DNA comprising modified nucleotides and/or modified polynucleotides, such as, though not limited to, methylated, protected and/or capped nucleotides or polynucleotides. The terms encompass poly- or oligo-ribonucleotides (RNA) and poly- or oligo-deoxyribonucleotides (DNA); RNA or DNA derived from N-glycosides or C-glycosides of nucleobases and/or modified nucleobases; nucleic acids derived from sugars and/or modified sugars; and nucleic acids derived from phosphate bridges and/or modified internucleotidic linkages. The term encompasses nucleic acids containing any combinations of nucleobases, modified nucleobases, sugars, modified sugars, phosphate bridges or modified internucleotidic linkages. Examples include, and are not limited to, nucleic acids containing ribose moieties, nucleic acids containing deoxy-ribose moieties, nucleic acids containing both ribose and deoxyribose moieties, nucleic acids containing ribose and modified ribose moieties. Unless otherwise specified, the prefix poly- refers to a nucleic acid containing 2 to about 10,000 nucleotide monomer units and wherein the prefix oligo- refers to a nucleic acid containing 2 to about 200 nucleotide monomer units.

[00143] Nucleobase: The term "nucleobase" refers to the parts of nucleic acids that are involved in the hydrogen-bonding that binds one nucleic acid strand to another complementary strand in a sequence specific manner. The most common naturally-occurring nucleobases are adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, a naturally-occurring nucleobases are modified adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a naturally-occurring nucleobases are methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a nucleobase comprises a heteroaryl ring wherein a ring atom is nitrogen, and when in a nucleoside, the nitrogen is bonded to a sugar moiety. In some embodiments, a nucleobase comprises a heterocyclic ring wherein a ring atom is nitrogen, and when in a nucleoside, the nitrogen is bonded to a sugar moiety. In some embodiments, a nucleobase is a "modified nucleobase," a nucleobase other than adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, a modified nucleobase is substituted A, T, C, G or U. In some embodiments, a modified nucleobase is a substituted tautomer of A, T, C, G, or U. In some embodiments, a modified nucleobases is methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a modified nucleobase mimics the spatial arrangement, electronic properties, or some other physicochemical property of the nucleobase and retains the property of hydrogen-bonding that binds one nucleic acid strand to another in a sequence specific manner. In some embodiments, a modified nucleobase can pair with all of the five naturally occurring bases (uracil, thymine, adenine, cytosine, or guanine) without substantially affecting the melting behavior, recognition by intracellular enzymes or activity of the oligonucleotide duplex. As used herein, the term "nucleobase" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleobases and nucleobase analogs. In some embodiments, a nucleobase is optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G, or U. In some embodiments, a "nucleobase" refers to a nucleobase unit in an oligonucleotide or a nucleic acid (e.g., A, T, C,

G or U as in an oligonucleotide or a nucleic acid).

[00144] Nucleoside: The term "nucleoside" refers to a moiety wherein a nucleobase or a modified nucleobase is covalently bound to a sugar or a modified sugar. In some embodiments, a nucleoside is a natural nucleoside, e.g., adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, or deoxycytidine. In some embodiments, a nucleoside is a modified nucleoside, e.g., a substituted natural nucleoside selected from adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, and deoxycytidine. In some embodiments, a nucleoside is a modified nucleoside, e.g., a substituted tautomer of a natural nucleoside selected from adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, and deoxycytidine. In some embodiments, a "nucleoside" refers to a nucleoside unit in an oligonucleotide or a nucleic acid.

[00145] Nucleotide: The term "nucleotide" as used herein refers to a monomeric unit of a polynucleotide that consists of a nucleobase, a sugar, and one or more internucleotidic linkages (e.g., phosphate linkages in natural DNA and RNA). The naturally occurring bases [guanine, (G), adenine, (A), cytosine, (C), thymine, (T), and uracil (U)] are derivatives of purine or pyrimidine, though it should be understood that naturally and non-naturally occurring base analogs are also included. The naturally occurring sugar is the pentose (five-carbon sugar) deoxyribose (which forms DNA) or ribose (which forms RNA), though it should be understood that naturally and non-naturally occurring sugar analogs are also included. Nucleotides are linked via internucleotidic linkages to form nucleic acids, or polynucleotides. Many internucleotidic linkages are known in the art (such as, though not limited to, phosphate, phosphorothioates, boranophosphates and the like). Artificial nucleic acids include PNAs (peptide nucleic acids), phosphotriesters, phosphorothionates, H-phosphonates, phosphoramidates, boranophosphates, methylphosphonates, phosphonoacetates, thiophosphonoacetates and other variants of the phosphate backbone of native nucleic acids, such as those described herein. In some embodiments, a natural nucleotide comprises a naturally occurring base, sugar and internucleotidic linkage. As used herein, the term "nucleotide" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleotides and nucleotide analogs. In some embodiments, a "nucleotide" refers to a nucleotide unit in an oligonucleotide or a nucleic acid.

[00146] Oligonucleotide: The term "oligonucleotide" refers to a polymer or oligomer of nucleotides, and may contain any combination of natural and non-natural nucleobases, sugars, and internucleotidic linkages.

[00147] Oligonucleotides can be single-stranded or double-stranded. A single-stranded oligonucleotide can have double-stranded regions (formed by two portions of the single-stranded oligonucleotide) and a double-stranded oligonucleotide, which comprises two oligonucleotide chains, can have single-stranded regions for example, at regions where the two oligonucleotide chains are not complementary to each other. Example oligonucleotides include, but are not limited to structural genes, genes including control and termination regions, self-replicating systems such as viral or plasmid DNA, single-stranded and double-stranded RNAi agents and other RNA interference reagents (RNAi agents or iRNA agents), shRNA, antisense oligonucleotides, ribozymes, microRNAs, microRNA mimics, supermirs, aptamers, antimirs, antagomirs, Ul

adaptors, triplex-forming oligonucleotides, G-quadruplex oligonucleotides, RNA activators, immuno-stimulatory oligonucleotides, and decoy oligonucleotides.

[00148] Oligonucleotides of the present disclosure can be of various lengths. In particular embodiments, oligonucleotides can range from about 2 to about 200 nucleosides in length. In various related embodiments, oligonucleotides, single-stranded, double-stranded, or triple-stranded, can range in length from about 4 to about 10 nucleosides, from about 10 to about 50 nucleosides, from about 20 to about 50 nucleosides, from about 15 to about 30 nucleosides, from about 20 to about 30 nucleosides in length. In some embodiments, an oligonucleotide is from about 9 to about 39 nucleosides in length. In some embodiments, an oligonucleotide is from about 25 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 26 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 27 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 28 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 29 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 30 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 31 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 32 to about 70 nucleosides in length. In some embodiments, an oligonucleotide is from about 25 to about 60 nucleosides in length. In some embodiments, an oligonucleotide is from about 25 to about 50 nucleosides in length. In some embodiments, an oligonucleotide is from about 25 to about 40 nucleosides in length. In some embodiments, an oligonucleotide is from about 30 to about 40 nucleosides in length. In some embodiments, the oligonucleotide is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleosides in length. In some embodiments, an oligonucleotide is at least 4 nucleosides in length. In some embodiments, an oligonucleotide is at least 5 nucleosides in length. In some embodiments, an oligonucleotide is at least 6 nucleosides in length. In some embodiments, an oligonucleotide is at least 7 nucleosides in length. In some embodiments, an oligonucleotide is at least 8 nucleosides in length. In some embodiments, an oligonucleotide is at least 9 nucleosides in length. In some embodiments, an oligonucleotide is at least 10 nucleosides in length. In some embodiments, an oligonucleotide is at least 11 nucleosides in length. In some embodiments, an oligonucleotide is at least 12 nucleosides in length. In some embodiments, an oligonucleotide is at least 15 nucleosides in length. In some embodiments, an oligonucleotide is at least 15 nucleosides in length. In some embodiments, an oligonucleotide is at least 16 nucleosides in length. In some embodiments, an oligonucleotide is at least 17 nucleosides in length. In some embodiments, an oligonucleotide is at least 18 nucleosides in length. In some embodiments, an oligonucleotide is at least 19 nucleosides in length. In some embodiments, an oligonucleotide is at least 20 nucleosides in length. In some embodiments, an oligonucleotide is at least 25 nucleosides in length. In some embodiments, an oligonucleotide is at least 26 nucleosides in length. In some embodiments, an oligonucleotide is at least 27 nucleosides in length. In some embodiments, an oligonucleotide is at least 28 nucleosides in length. In some embodiments, an oligonucleotide is at least 29 nucleosides in length. In some embodiments, an oligonucleotide is at least 30 nucleosides in length. In some embodiments, an oligonucleotide is at least 31 nucleosides in length. In some

embodiments, an oligonucleotide is at least 32 nucleosides in length. In some embodiments, an oligonucleotide is at least 33 nucleosides in length. In some embodiments, an oligonucleotide is at least 34 nucleosides in length. In some embodiments, an oligonucleotide is at least 35 nucleosides in length. In some embodiments, an oligonucleotide is at least 36 nucleosides in length. In some embodiments, an oligonucleotide is at least 37 nucleosides in length. In some embodiments, an oligonucleotide is at least 38 nucleosides in length. In some embodiments, an oligonucleotide is at least 39 nucleosides in length. In some embodiments, an oligonucleotide is at least 40 nucleosides in length. In some embodiments, an oligonucleotide is 25 nucleosides in length. In some embodiments, an oligonucleotide is 26 nucleosides in length. In some embodiments, an oligonucleotide is 27 nucleosides in length. In some embodiments, an oligonucleotide is 28 nucleosides in length. In some embodiments, an oligonucleotide is 29 nucleosides in length. In some embodiments, an oligonucleotide is 30 nucleosides in length. In some embodiments, an oligonucleotide is 31 nucleosides in length. In some embodiments, an oligonucleotide is 32 nucleosides in length. In some embodiments, an oligonucleotide is 33 nucleosides in length. In some embodiments, an oligonucleotide is 34 nucleosides in length. In some embodiments, an oligonucleotide is 35 nucleosides in length. In some embodiments, an oligonucleotide is 36 nucleosides in length. In some embodiments, an oligonucleotide is 37 nucleosides in length. In some embodiments, an oligonucleotide is 38 nucleosides in length. In some embodiments, an oligonucleotide is 39 nucleosides in length. In some embodiments, an oligonucleotide is 40 nucleosides in length. In some embodiments, each nucleoside counted in an oligonucleotide length independently comprises a nucleobase comprising a ring having at least one nitrogen ring atom. In some embodiments, each nucleoside counted in an oligonucleotide length independently comprises A, T, C, G, or U, or optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G or U.

[00149] Oligonucleotide type: As used herein, the phrase "oligonucleotide type" is used to define an oligonucleotide that has a particular base sequence, pattern of backbone linkages (i.e., pattern of internucleotidic linkage types, for example, phosphate, phosphorothioate, phosphorothioate triester, etc.), pattern of backbone chiral centers [i.e., pattern of linkage phosphorus stereochemistry (Rp/Sp)], and pattern of backbone phosphorus modifications. In some embodiments, oligonucleotides of a common designated "type" are structurally identical to one another.

[00150] One of skill in the art will appreciate that synthetic methods of the present disclosure provide for a degree of control during the synthesis of an oligonucleotide strand such that each nucleotide unit of the oligonucleotide strand can be designed and/or selected in advance to have a particular stereochemistry at the linkage phosphorus and/or a particular modification at the linkage phosphorus, and/or a particular base, and/or a particular sugar. In some embodiments, an oligonucleotide strand is designed and/or selected in advance to have a particular combination of stereocenters at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or determined to have a particular combination of modifications at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or selected to have a particular combination of bases. In some embodiments, an oligonucleotide strand is designed and/or selected

to have a particular combination of one or more of the above structural characteristics. In some embodiments, the present disclosure provides compositions comprising or consisting of a plurality of oligonucleotide molecules (e.g., chirally controlled oligonucleotide compositions). In some embodiments, all such molecules are of the same type (i.e., are structurally identical to one another). In some embodiments, however, provided compositions comprise a plurality of oligonucleotides of different types, typically in pre-determined relative amounts.

[00151] Optionally Substituted: As described herein, compounds, e.g., oligonucleotides, of the disclosure may contain optionally substituted and/or substituted moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. In some embodiments, an optionally substituted group is unsubstituted. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein. Certain substituents are described below.

[00152] Suitable monovalent substituents on a substitutable atom, e.g., a suitable carbon atom, are independently halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R^o$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; $-N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR°$, $-SC(S)SR°$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-Si(R°)_3$; $-OSi(R°)_3$; $-B(R°)_2$; $-OB(R°)_2$; $-OB(OR°)_2$; $-P(R°)_2$; $-P(OR°)_2$; $-P(R°)(OR°)$; $-OP(R°)_2$; $-OP(OR°)_2$; $-OP(R°)(OR°)$; $-P(O)(R°)_2$; $-P(O)(OR°)_2$; $-OP(O)(R°)_2$; $-OP(O)(OR°)_2$; $-OP(O)(OR°)(SR°)$; $-SP(O)(R°)_2$; $-SP(O)(OR°)_2$; $-N(R°)P(O)(R°)_2$; $-N(R°)P(O)(OR°)_2$; $-P(R°)_2[B(R°)_3]$; $-P(OR°)_2[B(R°)_3]$; $-OP(R°)_2[B(R°)_3]$; $-OP(OR°)_2[B(R°)_3]$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R°)_2$, wherein each R° may be substituted as defined herein and is independently hydrogen, C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1–5 heteroatoms independently selected from nitrogen,

oxygen, sulfur, silicon and phosphorus, $-CH_2-(C_{6-14}$ aryl), $-O(CH_2)_{0-1}(C_{6-14}$ aryl), $-CH_2$-(5-14 membered heteroaryl ring), a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, which may be substituted as defined below.

[00153] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, -C(O)SR$^\bullet$, $-(C_{1-4}$ straight or branched alkylene)C(O)OR$^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, and a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00154] Suitable divalent substituents, e.g., on a suitable carbon atom, are independently the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, and aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00155] Suitable substituents on the aliphatic group of R^* are independently halogen, $-R^\bullet$, -(haloR$^\bullet$), $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00156] In some embodiments, suitable substituents on a substitutable nitrogen are independently $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or,

notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00157] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $-OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00158] P-modification: as used herein, the term "P-modification" refers to any modification at the linkage phosphorus other than a stereochemical modification. In some embodiments, a P-modification comprises addition, substitution, or removal of a pendant moiety covalently attached to a linkage phosphorus.

[00159] Partially unsaturated: As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[00160] Pharmaceutical composition: As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, an active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[00161] Pharmaceutically acceptable: As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00162] Pharmaceutically acceptable carrier: As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound

from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[00163] Pharmaceutically acceptable salt: The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salt include, but are not limited to, nontoxic acid addition salts, which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, a provided compound comprises one or more acidic groups, e.g., an oligonucleotide, and a pharmaceutically acceptable salt is an alkali, alkaline earth metal, or ammonium (e.g., an ammonium salt of $N(R)_3$, wherein each R is independently defined and described in the present disclosure) salt. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, a pharmaceutically acceptable salt is a sodium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a pharmaceutically acceptable salt is a calcium salt. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary

ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate. In some embodiments, a provided compound comprises more than one acid groups, for example, an oligonucleotide may comprise two or more acidic groups (e.g., in natural phosphate linkages and/or modified internucleotidic linkages). In some embodiments, a pharmaceutically acceptable salt, or generally a salt, of such a compound comprises two or more cations, which can be the same or different. In some embodiments, in a pharmaceutically acceptable salt (or generally, a salt), all ionizable hydrogen (e.g., in an aqueous solution with a pKa no more than about 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2; in some embodiments, no more than about 7; in some embodiments, no more than about 6; in some embodiments, no more than about 5; in some embodiments, no more than about 4; in some embodiments, no more than about 3) in the acidic groups are replaced with cations. In some embodiments, each phosphorothioate and phosphate group independently exists in its salt form (e.g., if sodium salt, −O−P(O)(SNa)−O− and −O−P(O)(ONa)−O−, respectively). In some embodiments, each phosphorothioate and phosphate internucleotidic linkage independently exists in its salt form (e.g., if sodium salt, −O−P(O)(SNa)−O− and −O−P(O)(ONa)−O−, respectively). In some embodiments, a pharmaceutically acceptable salt is a sodium salt of an oligonucleotide. In some embodiments, a pharmaceutically acceptable salt is a sodium salt of an oligonucleotide, wherein each acidic phosphate and modified phosphate group (e.g., phosphorothioate, phosphate, etc.), if any, exists as a salt form (all sodium salt).

[00164] Predetermined: By predetermined (or pre-determined) is meant deliberately selected or non-random or controlled, for example as opposed to randomly occurring, random, or achieved without control. Those of ordinary skill in the art, reading the present specification, will appreciate that the present disclosure provides technologies that permit selection of particular chemistry and/or stereochemistry features to be incorporated into oligonucleotide compositions, and further permits controlled preparation of oligonucleotide compositions having such chemistry and/or stereochemistry features. Such provided compositions are "predetermined" as described herein. Compositions that may contain certain oligonucleotides because they happen to have been generated through a process that are not controlled to intentionally generate the particular chemistry and/or stereochemistry features are not "predetermined" compositions. In some embodiments, a predetermined composition is one that can be intentionally reproduced (e.g., through repetition of a controlled process). In some embodiments, a predetermined level of a plurality of oligonucleotides in a composition means that the absolute amount, and/or the relative amount (ratio, percentage, etc.) of the plurality of oligonucleotides in the composition is controlled. In some embodiments, a predetermined level of a plurality of oligonucleotides in a composition is achieved through chirally controlled oligonucleotide preparation.

[00165] Protecting group: The term "protecting group," as used herein, is well known in the art and includes those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Also included are those protecting groups specially adapted for nucleoside and nucleotide chemistry described in Current Protocols in Nucleic Acid Chemistry, edited by Serge L. Beaucage et al. 06/2012, the entirety of Chapter 2 is

incorporated herein by reference. Suitable amino–protecting groups include methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–t–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–t–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–t–butylphenyl)–1–methylethyl carbamate (t–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(N,N–dicyclohexylcarboxamido)ethyl carbamate, t–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, N–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p–methoxybenzyl carbamate (Moz), p–nitobenzyl carbamate, p–bromobenzyl carbamate, p–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(p–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, m–chloro–p–acyloxybenzyl carbamate, p–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), m–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, o–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(o–nitrophenyl)methyl carbamate, phenothiazinyl–(10)–carbonyl derivative, N'–p–toluenesulfonylaminocarbonyl derivative, N'–phenylaminothiocarbonyl derivative, t–amyl carbamate, S–benzyl thiocarbamate, p–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p–decyloxybenzyl carbamate, 2,2–dimethoxycarbonylvinyl carbamate, o–(N,N–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(N,N–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p–(p'–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(p–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, p–(phenylazo)benzyl carbamate, 2,4,6–tri–t–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, 2,4,6–trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, N–benzoylphenylalanyl derivative, benzamide, p–phenylbenzamide, o–nitophenylacetamide, o–nitrophenoxyacetamide, acetoacetamide, (N'–dithiobenzyloxycarbonylamino)acetamide, 3–(p–hydroxyphenyl)propanamide, 3–(o–

nitrophenyl)propanamide, 2–methyl–2–(o–nitrophenoxy)propanamide, 2–methyl–2–(o–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, o–nitrocinnamide, N–acetylmethionine derivative, o–nitrobenzamide, o–(benzoyloxymethyl)benzamide, 4,5–diphenyl–3–oxazolin–2–one, N–phthalimide, N–dithiasuccinimide (Dts), N–2,3–diphenylmaleimide, N–2,5–dimethylpyrrole, N–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, N–methylamine, N–allylamine, N–[2–(trimethylsilyl)ethoxy]methylamine (SEM), N–3–acetoxypropylamine, N–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, N–benzylamine, N–di(4–methoxyphenyl)methylamine, N–5–dibenzosuberylamine, N–triphenylmethylamine (Tr), N–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), N–9–phenylfluorenylamine (PhF), N–2,7–dichloro–9–fluorenylmethyleneamine, N–ferrocenylmethylamino (Fcm), N–2–picolylamino N'–oxide, N–1,1–dimethylthiomethyleneamine, N–benzylideneamine, N–p–methoxybenzylideneamine, N–diphenylmethyleneamine, N–[(2–pyridyl)mesityl]methyleneamine, N–(N',N'–dimethylaminomethylene)amine, N,N'–isopropylidenediamine, N–p–nitrobenzylideneamine, N–salicylideneamine, N–5–chlorosalicylideneamine, N–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, N–cyclohexylideneamine, N–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, N–borane derivative, N–diphenylborinic acid derivative, N–[phenyl(pentacarbonylchromium– or tungsten)carbonyl]amine, N–copper chelate, N–zinc chelate, N–nitroamine, N–nitrosoamine, amine N–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3–nitropyridinesulfenamide (Npys), p–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[00166] Suitably protected carboxylic acids further include, but are not limited to, silyl–, alkyl–, alkenyl–, aryl–, and arylalkyl–protected carboxylic acids. Examples of suitable silyl groups include trimethylsilyl, triethylsilyl, t–butyldimethylsilyl, t–butyldiphenylsilyl, triisopropylsilyl, and the like. Examples of suitable alkyl groups include methyl, benzyl, p–methoxybenzyl, 3,4–dimethoxybenzyl, trityl, t–butyl, tetrahydropyran–2–yl. Examples of suitable alkenyl groups include allyl. Examples of suitable aryl groups include optionally substituted phenyl, biphenyl, or naphthyl. Examples of suitable arylalkyl groups include optionally substituted benzyl (e.g., p–methoxybenzyl (MPM), 3,4–dimethoxybenzyl, O–nitrobenzyl, p–nitrobenzyl, p–halobenzyl,

2,6–dichlorobenzyl, p–cyanobenzyl), and 2– and 4–picolyl.

[00167] Suitable hydroxyl protecting groups include methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), t–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (p–AOM), guaiacolmethyl (GUM), t–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, t–butyl, allyl, p–chlorophenyl, p–methoxyphenyl, 2,4–dinitrophenyl, benzyl, p–methoxybenzyl, 3,4–dimethoxybenzyl, o–nitrobenzyl, p–nitrobenzyl, p–halobenzyl, 2,6–dichlorobenzyl, p–cyanobenzyl, p–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl N–oxido, diphenylmethyl, p,p'–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, p–methoxyphenyldiphenylmethyl, di(p–methoxyphenyl)phenylmethyl, tri(p–methoxyphenyl)methyl, 4–(4'–bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4',4''–tris(levulinoyloxyphenyl)methyl, 4,4',4''–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4',4''–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1'–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t–butyldimethylsilyl (TBDMS), t–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–p–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, p–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl p–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl p–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl o–nitrobenzyl carbonate, alkyl p–nitrobenzyl carbonate, alkyl S–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, o–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–

methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)–2–methyl–2–butenoate, o–(methoxycarbonyl)benzoate, α–naphthoate, nitrate, alkyl N,N,N',N'–tetramethylphosphorodiamidate, alkyl N–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2– or 1,3–diols, the protecting groups include methylene acetal, ethylidene acetal, 1–t–butylethylidene ketal, 1–phenylethylidene ketal, (4–methoxyphenyl)ethylidene acetal, 2,2,2–trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, p–methoxybenzylidene acetal, 2,4–dimethoxybenzylidene ketal, 3,4–dimethoxybenzylidene acetal, 2–nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1–methoxyethylidene ortho ester, 1–ethoxyethylidine ortho ester, 1,2–dimethoxyethylidene ortho ester, α–methoxybenzylidene ortho ester, 1–(N,N–dimethylamino)ethylidene derivative, α–(N,N'–dimethylamino)benzylidene derivative, 2–oxacyclopentylidene ortho ester, di–t–butylsilylene group (DTBS), 1,3–(1,1,3,3–tetraisopropyldisiloxanylidene) derivative (TIPDS), tetra–t–butoxydisiloxane–1,3–diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate.

[00168] In some embodiments, a hydroxyl protecting group is acetyl, t-butyl, tbutoxymethyl, methoxymethyl, tetrahydropyranyl, 1 -ethoxyethyl, 1 -(2-chloroethoxy)ethyl, 2- trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyl, p-phenylbenzoyl, 2,6- dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4,4'-dimethoxytrityl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetyl, trichloroacetyl, trifiuoroacetyl, pivaloyl, 9- fluorenylmethyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl, (DMTr) and 4,4',4"-trimethoxytrityl (TMTr), 2-cyanoethyl (CE or Cne), 2-(trimethylsilyl)ethyl (TSE), 2-(2-nitrophenyl)ethyl, 2-(4-cyanophenyl)ethyl 2-(4-nitrophenyl)ethyl (NPE), 2-(4-nitrophenylsulfonyl)ethyl, 3,5-dichlorophenyl, 2,4-dimethylphenyl, 2-nitrophenyl, 4-nitrophenyl, 2,4,6-trimethylphenyl, 2-(2-nitrophenyl)ethyl, butylthiocarbonyl, 4,4',4"-tris(benzoyloxy)trityl, diphenylcarbamoyl, levulinyl, 2-(dibromomethyl)benzoyl (Dbmb), 2-(isopropylthiomethoxymethyl)benzoyl (Ptmt), 9-phenylxanthen-9-yl (pixyl) or 9-(p-methoxyphenyl)xanthine-9-y1 (MOX). In some embodiments, each of the hydroxyl protecting groups is, independently selected from acetyl, benzyl, t- butyldimethylsilyl, t-butyldiphenylsilyl and 4,4'-dimethoxytrityl. In some embodiments, the hydroxyl protecting group is selected from the group consisting of trityl, monomethoxytrityl and 4,4'-dimethoxytrityl group. In some embodiments, a phosphorous linkage protecting group is a group attached to the phosphorous linkage (e.g., an internucleotidic linkage) throughout oligonucleotide synthesis. In some embodiments, a protecting group is attached to a sulfur atom of an phosphorothioate group. In some embodiments, a protecting group is attached to an oxygen atom of an internucleotide phosphorothioate linkage. In some embodiments, a protecting group is attached to an oxygen atom of the internucleotide phosphate linkage. In some embodiments a protecting group is 2-

cyanoethyl (CE or Cne), 2-trimethylsilylethyl, 2-nitroethyl, 2-sulfonylethyl, methyl, benzyl, o-nitrobenzyl, 2-(p-nitrophenyl)ethyl (NPE or Npe), 2-phenylethyl, 3-(N-tert-butylcarboxamido)-1-propyl, 4-oxopentyl, 4-methylthio-l-butyl, 2-cyano-1,1-dimethylethyl, 4-N-methylaminobutyl, 3-(2-pyridyl)-1-propyl, 2-[N-methyl-N-(2-pyridyl)]aminoethyl, 2-(N-formyl,N-methyl)aminoethyl, or 4-[N-methyl-N-(2,2,2-trifluoroacetyl)amino]butyl.

[00169] Subject: As used herein, the term "subject" or "test subject" refers to any organism to which a compound (e.g., an oligonucleotide) or composition is administered in accordance with the present disclosure e.g., for experimental, diagnostic, prophylactic and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; etc.) and plants. In some embodiments, a subject is a human. In some embodiments, a subject may be suffering from and/or susceptible to a disease, disorder and/or condition.

[00170] Substantially: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. A base sequence which is substantially identical or complementary to a second sequence is not fully identical or complementary to the second sequence, but is mostly or nearly identical or complementary to the second sequence. In some embodiments, an oligonucleotide with a substantially complementary sequence to another oligonucleotide or nucleic acid forms duplex with the oligonucleotide or nucleic acid in a similar fashion as an oligonucleotide with a fully complementary sequence. In addition, one of ordinary skill in the biological and/or chemical arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and/or chemical phenomena.

[00171] Sugar: The term "sugar" refers to a monosaccharide or polysaccharide in closed and/or open form. In some embodiments, sugars are monosaccharides. In some embodiments, sugars are polysaccharides. Sugars include, but are not limited to, ribose, deoxyribose, pentofuranose, pentopyranose, and hexopyranose moieties. As used herein, the term "sugar" also encompasses structural analogs used in lieu of conventional sugar molecules, such as glycol, polymer of which forms the backbone of the nucleic acid analog, glycol nucleic acid ("GNA"), etc. As used herein, the term "sugar" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified sugars and nucleotide sugars. In some embodiments, a sugar is a RNA or DNA sugar (ribose or deoxyribose). In some embodiments, a sugar is a modified ribose or deoxyribose sugar, e.g., 2'-modified, 5'-modified, etc. As described herein, in some embodiments, when used in oligonucleotides and/or nucleic acids, modified sugars may provide one or more desired properties, activities, etc. In some embodiments, a sugar is optionally substituted ribose or deoxyribose. In some embodiments, a "sugar" refers to a sugar unit in an oligonucleotide or a nucleic acid.

[00172] Susceptible to: An individual who is "susceptible to" a disease, disorder and/or condition is one who has a higher risk of developing the disease, disorder and/or condition than does a member of the general public. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition is

predisposed to have that disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not have been diagnosed with the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[00173] Therapeutic agent: As used herein, the term "therapeutic agent" in general refers to any agent that elicits a desired effect (e.g., a desired biological, clinical, or pharmacological effect) when administered to a subject. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, an appropriate population is a population of subjects suffering from and/or susceptible to a disease, disorder or condition. In some embodiments, an appropriate population is a population of model organisms. In some embodiments, an appropriate population may be defined by one or more criterion such as age group, gender, genetic background, preexisting clinical conditions, prior exposure to therapy. In some embodiments, a therapeutic agent is a substance that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms or features of a disease, disorder, and/or condition in a subject when administered to the subject in an effective amount. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans. In some embodiments, a therapeutic agent is a provided compound, e.g., a provided oligonucleotide.

[00174] Therapeutically effective amount: As used herein, the term "therapeutically effective amount" means an amount of a substance (e.g., a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[00175] Treat: As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[00176] Unsaturated: The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[00177] Wild-type: As used herein, the term "wild-type" has its art-understood meaning that refers to an entity having a structure and/or activity as found in nature in a "normal" (as contrasted with mutant, diseased, altered, etc.) state or context. Those of ordinary skill in the art will appreciate that wild type genes and polypeptides often exist in multiple different forms (e.g., alleles).

[00178] As those skilled in the art will appreciate, methods and compositions described herein relating to provided compounds (e.g., oligonucleotides) generally also apply to pharmaceutically acceptable salts of such compounds.

Description of Certain Embodiments

[00179] Oligonucleotides are useful in various therapeutic, diagnostic, and research applications. Use of naturally occurring nucleic acids is limited, for example, by their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings and/or to further improve various properties and activities. These include synthetic oligonucleotides that contain chemical modifications, e.g., base modifications, sugar modifications, backbone modifications, etc., which, among other things, render these molecules less susceptible to degradation and improve other properties and/or activities.

[00180] From a structural point of view, modifications to internucleotidic linkages can introduce chirality, and certain properties and activities may be affected by configurations of linkage phosphorus atoms of oligonucleotides. For example, binding affinity, sequence specific binding to complementary RNA, stability to nucleases, activities, delivery, pharmacokinetics, etc. can be affected by, inter alia, chirality of backbone linkage phosphorus atoms.

[00181] Among other things, the present disclosure utilizes technologies for controlling various structural elements, e.g., sugar modifications and patterns thereof, nucleobase modifications and patterns thereof, modified internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, additional chemical moieties (moieties that are not typically in an oligonucleotide chain) and patterns thereof, etc. With the capability to fully control structural elements of oligonucleotides, the present disclosure provides oligonucleotides with improved and/or new properties and/or activities for various applications, e.g.,

as therapeutic agents, probes, etc. For example, as demonstrated herein, provided oligonucleotides and compositions thereof are particularly powerful for editing target adenosine in target nucleic acids to, in some embodiments, correct a G to A mutation by converting A to I.

[00182] In some embodiments, an oligonucleotide comprises a sequence that is identical to or is completely or substantially complementary to 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, typically 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 or more, contiguous bases of a nucleic acid (e.g., DNA, pre-mRNA, mRNA, etc.). In some embodiments, a nucleic acid is a target nucleic acid comprising one or more target adenosine. In some embodiments, a target nucleic acid comprises one and no more than one target adenosine. In some embodiments, an oligonucleotide can hybridize with a target nucleic acid. In some embodiments, such hybridization facilitates modification of A (e.g.,, conversion of A to I) by, e.g., ADAR1, ADAR2, etc., in a nucleic acid or a product thereof.

[00183] In some embodiments, the present disclosure provides an oligonucleotide, wherein the oligonucleotide has a base sequence which is, or comprises about 10-40, about 15-40, about 20-40, or at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34 contiguous bases of, an oligonucleotide or nucleic acid disclosed herein (e.g., in the Tables), or a sequence that is complementary to a target RNA sequence gene, transcript, etc. disclosed herein, and wherein each T can be optionally and independently replaced with U and vice versa. In some embodiments, the present disclosure provides an oligonucleotide or oligonucleotide composition as disclosed herein, e.g., in a Table.

[00184] In some embodiments, an oligonucleotide is a single-stranded oligonucleotide for site-directed editing of a nucleoside (e.g., a target adenosine) in a target nucleic acid, e.g., RNA.

[00185] As described herein, oligonucleotides may contain one or more modified internucleotidic linkages (non-natural phosphate linkages). In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage whose linkage phosphorus is chiral. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, oligonucleotides comprise one or more negatively charged internucleotidic linkages (e.g., phosphorothioate internucleotidic linkages, natural phosphate linkages, etc.). In some embodiments, oligonucleotides comprise one or more non-negatively charged internucleotidic linkage. In some embodiments, oligonucleotides comprise one or more neutral internucleotidic linkage.

[00186] In some embodiments, oligonucleotides are chirally controlled. In some embodiments, oligonucleotides are chirally pure (or "stereopure", "stereochemically pure"), wherein the oligonucleotide exists as a single stereoisomeric form (in many cases a single diastereoisomeric (or "diastereomeric") form as multiple chiral centers may exist in an oligonucleotide, e.g., at linkage phosphorus, sugar carbon, etc.). As appreciated by those skilled in the art, a chirally pure oligonucleotide is separated from its other stereoisomeric forms (to the extent that some impurities may exist as chemical and biological processes, selectivities and/or

purifications etc. rarely, if ever, go to absolute completeness). In a chirally pure oligonucleotide, each chiral center is independently defined with respect to its configuration (for a chirally pure oligonucleotide, each internucleotidic linkage is independently stereodefined or chirally controlled). In contrast to chirally controlled and chirally pure oligonucleotides which comprise stereodefined linkage phosphorus, racemic (or "stereorandom", "non-chirally controlled") oligonucleotides comprising chiral linkage phosphorus, e.g., from traditional phosphoramidite oligonucleotide synthesis without stereochemical control during coupling steps in combination with traditional sulfurization (creating stereorandom phosphorothioate internucleotidic linkages), refer to a random mixture of various stereoisomers (typically diastereoisomers (or "diastereomers") as there are multiple chiral centers in an oligonucleotide; *e.g.*, from traditional oligonucleotide preparation using reagents containing no chiral elements other than those in nucleosides and linkage phosphorus). For example, for A*A*A wherein * is a phosphorothioate internucleotidic linkage (which comprises a chiral linkage phosphorus), a racemic oligonucleotide preparation includes four diastereomers [$2^2 = 4$, considering the two chiral linkage phosphorus, each of which can exist in either of two configurations (*S*p or *R*p)]: A *S A *S A, A *S A *R A, A *R A *S A, and A *R A *R A, wherein *S represents a *S*p phosphorothioate internucleotidic linkage and *R represents a *R*p phosphorothioate internucleotidic linkage. For a chirally pure oligonucleotide, e.g., A *S A *S A, it exists in a single stereoisomeric form and it is separated from the other stereoisomers (e.g., the diastereomers A *S A *R A, A *R A *S A, and A *R A *R A).

[00187] In some embodiments, oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more stereorandom internucleotidic linkages (mixture of *R*p and *S*p linkage phosphorus at the internucleotidic linkage, e.g., from traditional non-chirally controlled oligonucleotide synthesis). In some embodiments, oligonucleotides comprise one or more (e.g., 1-60, 1-50, 1-40, 1-30, 1-25, 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 or more) chirally controlled internucleotidic linkages (*R*p or *S*p linkage phosphorus at the internucleotidic linkage, e.g., from chirally controlled oligonucleotide synthesis). In some embodiments, an internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage is a stereorandom phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage is a chirally controlled phosphorothioate internucleotidic linkage.

[00188] Among other things, the present disclosure provides technologies for preparing chirally controlled (in some embodiments, stereochemically pure) oligonucleotides. In some embodiments, oligonucleotides are stereochemically pure. In some embodiments, oligonucleotides of the present disclosure are about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% stereochemically pure.

[00189] In some embodiments, the present disclosure provides various oligonucleotide compositions. In

some embodiments, oligonucleotide compositions are stereorandom or not chirally controlled. In some embodiments, there are no chirally controlled internucleotidic linkages in oligonucleotides of provided compositions. In some embodiments, internucleotidic linkages of oligonucleotides in compositions comprise one or more chirally controlled internucleotidic linkages (e.g.,, chirally controlled oligonucleotide compositions).

[00190] In some embodiments, an oligonucleotide composition comprises a plurality of oligonucleotides sharing a common base sequence, wherein one or more internucleotidic linkages in the oligonucleotides are chirally controlled and one or more internucleotidic linkages are stereorandom (not chirally controlled). In some embodiments, an oligonucleotide composition comprises a plurality of oligonucleotides sharing a common base sequence, wherein each internucleotidic linkage comprising chiral linkage phosphorus in the oligonucleotides is independently a chirally controlled internucleotidic linkage. In some embodiments, a plurality of oligonucleotides share the same base sequence, and the same base and sugar modification. In some embodiments, a plurality of oligonucleotides share the same base sequence, and the same base, sugar and internucleotidic linkage modification. In some embodiments, an oligonucleotide composition comprises oligonucleotides of the same constitution, wherein one or more internucleotidic linkages are chirally controlled and one or more internucleotidic linkages are stereorandom (not chirally controlled). In some embodiments, an oligonucleotide composition comprises oligonucleotides of the same constitution, wherein each internucleotidic linkage comprising chiral linkage phosphorus is independently a chirally controlled internucleotidic linkage. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90% or 95% of all oligonucleotides, or all oligonucleotides of the common base sequence, are oligonucleotides of the plurality.

[00191] In some embodiments, the present disclosure provides technologies for preparing, assessing and/or utilizing provided oligonucleotides and compositions thereof.

[00192] As used in the present disclosure, in some embodiments, "one or more" is 1-200, 1-150, 1-100, 1-90, 1-80, 1-70, 1-60, 1-50, 1-40, 1-30, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60. In some embodiments, "one or more" is one. In some embodiments, "one or more" is two. In some embodiments, "one or more" is three. In some embodiments, "one or more" is four. In some embodiments, "one or more" is five. In some embodiments, "one or more" is six. In some embodiments, "one or more" is seven. In some embodiments, "one or more" is eight. In some embodiments, "one or more" is nine. In some embodiments, "one or more" is ten. In some embodiments, "one or more" is at least one. In some embodiments, "one or more" is at least two. In some embodiments, "one or more" is at least three. In some embodiments, "one or more" is at least four. In some embodiments, "one or more" is at least five. In some embodiments, "one or more" is at least six. In some embodiments, "one or more" is at least seven. In some embodiments, "one or more" is at least eight. In some embodiments, "one or more" is at least nine. In some embodiments, "one or more" is at least ten.

[00193] As used in the present disclosure, in some embodiments, "at least one" is one or more.

[00194] Various embodiments are described for variables, e.g., R, R^L, L, etc., as examples. Embodiments described for a variable, e.g., R, are generally applicable to all variables that can be such a variable (e.g., R', R", R^L, R^{L1}, etc.).

Oligonucleotides

[00195] Among other things, the present disclosure provides oligonucleotides of various designs, which may comprise various nucleobases and patterns thereof, sugars and patterns thereof, internucleotidic linkages and patterns thereof, and/or additional chemical moieties and patterns thereof as described in the present disclosure. In some embodiments, provided oligonucleotides can direct A to I editing in target nucleic acids. In some embodiments, oligonucleotides of the present disclosure are single-stranded oligonucleotides capable of site-directed editing of an adenosine (conversion of A into I) in a target RNA sequence.

[00196] In some embodiments, oligonucleotides are of suitable lengths and sequence complementarity to specifically hybridize with target nucleic acids. In some embodiments, oligonucleotide is sufficiently long and is sufficiently complementary to target nucleic acids to distinguish target nucleic acid from other nucleic acids to reduce off-target effects. In some embodiments, oligonucleotide is sufficiently short to facilitate delivery, reduce manufacture complexity and/or cost which maintaining desired properties and activities (e.g., editing of adenosine).

[00197] In some embodiments, an oligonucleotide has a length of about 10-200 (e.g., about 10-20, 10-30, 10-40, 10-50, 10-60, 10-70, 10-80, 10-90, 10-100, 10-120, 10-150, 20-30, 20-40, 20-50, 20-60, 20-70, 20-80, 20-90, 20-100, 20-120, 20-150, 20-200, 25-30, 25-40, 25-50, 25-60, 25-70, 25-80, 25-90, 25-100, 25-120, 25-150, 25-200, 30-40, 30-50, 30-60, 30-70, 30-80, 30-90, 30-100, 30-120, 30-150, 30-200, 10, 20, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 60, etc.) nucleobases. In some embodiments, the base sequence of an oligonucleotide is about 10-60 nucleobases in length. In some embodiments, a base sequence is about 15-50 nucleobases in length. In some embodiments, a base sequence is from about 15 to about 35 nucleobases in length. In some embodiments, a base sequence is from about 25 to about 34 nucleobases in length. In some embodiments, a base sequence is from about 26 to about 35 nucleobases in length. In some embodiments, a base sequence is from about 27 to about 32 nucleobases in length. In some embodiments, a base sequence is from about 29 to about 35 nucleobases in length. In some embodiments, a base sequence is about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 nucleobases in length. In some other embodiments, a base sequence is or is at least 35 nucleobases in length. In some other embodiments, a base sequence is or is at least 34 nucleobases in length. In some other embodiments, a base sequence is or is at least 33 nucleobases in length. In some other embodiments, a base sequence is or is at least 32 nucleobases in length. In some other embodiments, a base sequence is or is at least 31 nucleobases in length. In some other embodiments, a base sequence is or is at least 30 nucleobases in length. In some other

embodiments, a base sequence is or is at least 29 nucleobases in length. In some other embodiments, a base sequence is or is at least 28 nucleobases in length. In some other embodiments, a base sequence is or is at least 27 nucleobases in length. In some other embodiments, a base sequence is or is at least 26 nucleobases in length. In some other embodiments, the base sequence of the complementary portion in a duplex is at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 16, 27, 28, 29, 30, 31, 32, 33, 34, 35 or more nucleobases in length. In some other embodiments, it is at least 18 nucleobases in length. In some other embodiments, it is at least 19 nucleobases in length. In some other embodiments, it is at least 20 nucleobases in length. In some other embodiments, it is at least 21 nucleobases in length. In some other embodiments, it is at least 22 nucleobases in length. In some other embodiments, it is at least 23 nucleobases in length. In some other embodiments, it is at least 24 nucleobases in length. In some other embodiments, it is at least 25 nucleobases in length. Among other things, the present disclosure provides oligonucleotides of comparable or better properties and/or comparable or higher activities but of shorter lengths compared to prior reported adenosine editing oligonucleotides.

[00198] In some embodiments, a base sequence of the oligonucleotide is complementary to a base sequence of a target nucleic acid (e.g., complementarity to a portion of the target nucleic acid comprising the target adenosine) with 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches which are not Watson-Crick base pairs (AT, AU and CG). In some embodiments, there are no mismatches. In some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches. In some embodiments, oligonucleotides may contain portions that are not designed for complementarity (e.g., loops, protein binding sequences, etc., for recruiting of proteins, e.g., ADAR). As those skilled in the art will appreciate, when calculating mismatches and/or complementarity, such portions may be properly excluded. In some embodiments, complementarity, e.g., between oligonucleotides and target nucleic acids, is about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.). In some embodiments, complementarity is at least about 60%. In some embodiments, complementarity is at least about 65%. In some embodiments, complementarity is at least about 70%. In some embodiments, complementarity is at least about 75%. In some embodiments, complementarity is at least about 80%. In some embodiments, complementarity is at least about 85%. In some embodiments, complementarity is at least about 90%. In some embodiments, complementarity is at least about 95%. In some embodiments, complementarity is 100% across

the length of an oligonucleotide. In some embodiments, complementarity is 100% except at a nucleoside opposite to a target nucleoside (e.g., adenosine) across the length of an oligonucleotide. Typically, complementarity is based on Watson-Crick base pairs AT, AU and CG. Those skilled in the art will appreciate that when assessing complementarity of two sequences of different lengths (e.g., a provided oligonucleotide and a target nucleic acid) complementarity may be properly based on the length of the shorter sequence and/or maximum complementarity between the two sequences. In many embodiments, oligonucleotides and target nucleic acids are of sufficient complementarity such that modifications are selectively directed to target adenosine sites.

[00199] In some embodiments, one or more mismatches are independently wobbles. In some embodiments, each mismatch is a wobble. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, a wobble is G-U, I-A, G-A, I-U, I-C, I-T, A-A, or reverse A-T. In some embodiments, a wobble is G-U, I-A, G-A, I-U, or I-C. In some embodiments, I-C may be considered a match when I is a 3' immediate nucleoside next to a nucleoside opposite to a target nucleoside. In some embodiments, a base that forms a wobble pair (e.g., U which can form a G-U wobble) may replace a base that forms a match pair (e.g., C which matches G) and can provide oligonucleotide with editing activity.

[00200] In some embodiments, duplexes of oligonucleotides and target nucleic acids comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

[00201] In some embodiments, distances between two mismatches, mismatches and one or both ends of oligonucleotides (or a portion thereof, e.g., first domain, second domain, first subdomain, second subdomain, third subdomain), and/or mismatches and nucleosides opposite to target adenosine can independently be 0-50, 0-40, 0-30, 0-25, 0-20, 0-15, 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleobases (not including mismatches, end nucleosides and nucleosides opposite to target adenosine). In some embodiments, a number is 0-30. In some embodiments, a number is 0-20. In some embodiments, a number is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. In some embodiments, a distance between two mismatches is 0-20. In some embodiments, a distance between two mismatches is 1-10. In some

embodiments, a distance between a mismatch and a 5'-end nucleoside of an oligonucleotide is 0-20. In some embodiments, a distance between a mismatch and a 5'-end nucleoside of an oligonucleotide is 5-20. In some embodiments, a distance between a mismatch and a 3'-end nucleoside of an oligonucleotide is 0-40. In some embodiments, a distance between a mismatch and a 3'-end nucleoside of an oligonucleotide is 5-20. In some embodiments, a distance between a mismatch and a nucleoside opposite to a target adenosine is 0-20. In some embodiments, a distance between a mismatch and a nucleoside opposite to a target adenosine is 1-10. In some embodiments, the number of nucleobases for a distance is 0. In some embodiments, it is 1. In some embodiments, it is 2. In some embodiments, it is 3. In some embodiments, it is 4. In some embodiments, it is 5. In some embodiments, it is 6. In some embodiments, it is 7. In some embodiments, it is 8. In some embodiments, it is 9. In some embodiments, it is 10. In some embodiments, it is 11. In some embodiments, it is 12. In some embodiments, it is 13. In some embodiments, it is 14. In some embodiments, it is 15. In some embodiments, it is 16. In some embodiments, it is 17. In some embodiments, it is 18. In some embodiments, it is 19. In some embodiments, it is 20. In some embodiments, a mismatch is at an end, e.g., a 5'-end or 3'-end of a first domain, second domain, first subdomain, second subdomain, or third subdomain. In some embodiments, a mismatch is at a nucleoside opposite to a target adenosine.

[00202] In some embodiments, provided oligonucleotides can direct adenosine editing (e.g.,, converting A to I) in a target nucleic acid and has a base sequence which consists of, comprises, or comprises a portion (e.g., a span of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or more contiguous bases) of the base sequence of an oligonucleotide disclosed herein, wherein each T can be independently replaced with U and vice versa, and the oligonucleotide comprises at least one non-naturally-occurring modification of a base, sugar and/or internucleotidic linkage.

[00203] In some embodiments, a provided oligonucleotide comprises one or more carbohydrate moieties. In some embodiments, a provided oligonucleotide comprises one or more GalNAc moieties. In some embodiments, a provided oligonucleotide comprises one or more targeting moieties. Non-limiting examples of such additional chemical moieties which can be conjugated to oligonucleotide chain are described herein.

[00204] In some embodiments, provided oligonucleotides can direct a correction of a G to A mutation in a target sequence, or a product thereof. In some embodiments, a correction of a G to A mutation is or comprises conversion of A to I, which can be read as G during translation or other biological processes. In some embodiments, provided oligonucleotides can direct a correction of a G to A mutation in a target sequence or a product thereof via ADAR-mediated deamination. In some embodiments, provided oligonucleotides can direct a correction of a G to A mutation in a target sequence or a product thereof via ADAR-mediated deamination by recruiting an endogenous ADAR (e.g., in a target cell) and facilitating the ADAR-mediated deamination. Regardless, however, the present disclosure is not limited to any particular mechanism. In some embodiments, the present disclosure provides oligonucleotides, compositions, methods, etc., capable of operating via double-stranded RNA interference, single-stranded RNA interference, RNase H-mediated knock-down, steric hindrance of translation, ADAR-mediated deamination or a combination of two or more such mechanisms.

[00205] In some embodiments, an oligonucleotide comprises a structural element or a portion thereof described herein, e.g., in a Table. In some embodiments, an oligonucleotide has a base sequence which comprises the base sequence (or a portion thereof) wherein each T can be independently substituted with U, pattern of chemical modifications (or a portion thereof), and/or a format of an oligonucleotide disclosed herein, e.g., in a Table or in the Figures, or otherwise disclosed herein. In some embodiments, such oligonucleotide can direct a correction of a G to A mutation in a target sequence, or a product thereof.

[00206] Among other things, provided oligonucleotides may hybridize to their target nucleic acids (e.g., pre-mRNA, mature mRNA, etc.). In some embodiments, oligonucleotide can hybridize to a target RNA sequence nucleic acid in any stage of RNA processing, including but not limited to a pre-mRNA or a mature mRNA. In some embodiments, oligonucleotide can hybridize to any element of oligonucleotide nucleic acid or its complement, including but not limited to: a promoter region, an enhancer region, a transcriptional stop region, a translational start signal, a translation stop signal, a coding region, a non-coding region, an exon, an intron, an intron/exon or exon/intron junction, the 5' UTR, or the 3' UTR.

[00207] In some embodiments, oligonucleotide hybridizes to two or more variants of transcripts derived from a sense strand of a target site (e.g., a target sequence).

[00208] In some embodiments, provided oligonucleotides contain increased levels of one or more isotopes. In some embodiments, provided oligonucleotides are labeled, e.g., by one or more isotopes of one or more elements, e.g., hydrogen, carbon, nitrogen, etc. In some embodiments, provided oligonucleotides in provided compositions, e.g., oligonucleotides of a plurality of a composition, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications, wherein the oligonucleotides contain an enriched level of deuterium. In some embodiments, provided oligonucleotides are labeled with deuterium (replacing $-^{1}H$ with $-^{2}H$) at one or more positions. In some embodiments, one or more ^{1}H of an oligonucleotide chain or any moiety conjugated to the oligonucleotide chain (e.g., a targeting moiety, etc.) is substituted with ^{2}H. Such oligonucleotides can be used in compositions and methods described herein.

[00209] In some embodiments, oligonucleotides comprise one or more modified nucleobases, one or more modified sugars, and/or one or more modified internucleotidic linkages as described herein. In some embodiments, oligonucleotides comprise a certain level of modified nucleobases, modified sugars, and/or modified internucleotidic linkages, e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all nucleobases, sugars, and internucleotidic linkages, respectively, within an oligonucleotide.

[00210] In some embodiments, oligonucleotides comprise one or more modified sugars. In some embodiments, an oligonucleotide comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13,

14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars. In some embodiments, an oligonucleotide comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars with 2'-F modification. In some embodiments, an oligonucleotide comprises about 2-50 (e.g., about 2, 3, 4, 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., 2-40, 2-30, 2-25, 2-20, 2-15, 2-10, 3-40, 3-30, 3-25, 3-20, 3-15, 3-10, 4-40, 4-30, 4-25, 4-20, 4-15, 4-10, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 6-40, 6-30, 6-25, 6-20, 6-15, 6-10, 7-40, 7-30, 7-25, 7-20, 7-15, 7-10, 8-40, 8-30, 8-25, 8-20, 8-15, 8-10, 9-40, 9-30, 9-25, 9-20, 9-15, 9-10, 10-40, 10-30, 10-25, 10-20, 10-15, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) consecutive modified sugars with 2'-F modification. In some embodiments, an oligonucleotide comprises 2 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 3 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 4 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 5 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 6 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 7 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 8 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 9 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises 10 consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises two or more 2'-F modified sugar blocks, wherein each sugar in a 2'-F modified sugar block is independently a 2'-F modified sugar. In some embodiments, each 2'-F modified sugar block independently comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive 2'-F modified sugars as described herein. In some embodiments, two consecutive 2'-F modified sugar blocks are independently separated by a separating block which separating block comprises one or more sugars that are independently not 2'-F modified sugars. In some embodiments, an oligonucleotide comprises one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F blocks and one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) separating blocks. In some embodiments, a first domain comprises one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F blocks and one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) separating blocks. In some embodiments, each first domain block bonded to a first domain 2'-F block is a separating block. In some embodiments, each first domain block bonded to a first domain separating block is a first domain 2'-F block. In some embodiments, each sugar in a separating block is independently not 2'-F modified. In some embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10

or more) or all sugars in a separating block are independently not 2'-F modified. In some embodiments, a separating block comprises one or more bicyclic sugars (e.g., LNA sugar, cEt sugar, etc.) and/or one or more 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, a separating block comprises one or more 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, two or more non-2'-F modified sugars are consecutive. In some embodiments, two or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.) are consecutive. In some embodiments, a separating block comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, a separating block comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) consecutive 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE sugar. In some embodiments, a separating block comprises one or more 2'-F modified sugars. In some embodiments, none of 2'-F modified sugars in a separating block are next to each other. In some embodiments, a separating block contain no 2'-F modified sugars. In some embodiments, each sugar in a separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each sugar in each separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each sugar in a separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in each separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a separating block is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in each separating block is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in a separating block is independently a 2'-OMe modified sugar. In some embodiments, each sugar in a separating block is independently a 2'-MOE modified sugar. In some embodiments, a separating block comprises a 2'-OMe sugar and 2'-MOE modified sugar. In some embodiments, each 2'-F block and each separating block independently contains 1, 2, 3, 4, or 5 nucleosides. In some embodiments, each 2'-F block and each separating block independently contains 1, 2, or 3 nucleosides.

[00211] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are modified sugars. In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%,

60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are modified sugars independently selected from 2'-F modified sugars, 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic, and bicyclic sugars (e.g., LNA sugars, cEt sugars, etc.). In some embodiments, a percentage is about or at least about 30%. In some embodiments, a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%. In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00212] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are modified sugars independently selected from 2'-F modified sugars and 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are modified sugars independently selected from 2'-F modified sugars, 2'-OMe modified sugars and 2'-MOE modified sugars. In some embodiments, a percentage is about or at least about 30%. In some embodiments, a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%. In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00213] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are modified sugars independently selected from 2'-F modified sugars and 2'-OMe modified sugars. In some embodiments, a percentage is about or at least about 30%. In some embodiments,

a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%. In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00214] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-F modified sugars. In some embodiments, a percentage is about or at least about 30%. In some embodiments, a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%. In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%. In some embodiments, 10 or more (e.g., about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, 10-50, 10-40, 10-30, 10-25, 15-50, 15-40, 15-30, 15-25, 20-50, 20-40, 20-30, 20-25, etc.) sugars are 2'-F modified sugars. In some embodiments, an oligonucleotide comprises two or more (e.g., 2-30, 2-25, 2-20, 2-15, 3-10, 3-30, 3-25, 3-20, 3-15, 3-10, 4-30, 4-25, 4-20, 4-15, 4-10, 5-30, 5-25, 5-20, 5-15, 5-10, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises one or more 2'-F blocks each independently comprising two or more (e.g., 2-30, 2-25, 2-20, 2-15, 3-10, 3-30, 3-25, 3-20, 3-15, 3-10, 4-30, 4-25, 4-20, 4-15, 4-10, 5-30, 5-25, 5-20, 5-15, 5-10, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) consecutive 2'-F modified sugars. In some embodiments, an oligonucleotide comprises two or more 2'-F blocks as described herein separated by one or more separating blocks as described herein. In some embodiments, a 2'-F block has 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-F modified sugars. In some embodiments, a 2'-F block has no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 10 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 9 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 8 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 7 2'-F modified

sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 6 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 5 2'-F modified sugars. In some embodiments, each sugar in each 2'-F blocks is a 2'-F modified sugar, and each 2'-F block independently has no more than 4 2'-F modified sugars. In some embodiments, each block bonded to a 2'-F block is independently a block that comprises no 2'-F modified sugar. In some embodiments, each block bonded to a 2'-F block is independently a block that comprises a natural DNA or RNA sugar, a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each block bonded to a 2'-F block is independently a block that comprises a natural DNA or RNA sugar, a 2'-OMe modified sugar, 2'-MOE modified sugar or a bicyclic sugar. In some embodiments, each block bonded to a 2'-F block is independently a block that comprises a natural DNA or RNA sugar, a 2'-OMe modified sugar or 2'-MOE modified sugar. In some embodiments, each nucleoside in a first domain bonded to a 2'-F block in a first domain is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each nucleoside in a first domain bonded to a 2'-F block in a first domain is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each nucleoside in a first domain bonded to a 2'-F block in a first domain is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each nucleoside in a second domain bonded to a 2'-F block in a second domain is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each nucleoside in a second domain bonded to a 2'-F block in a second domain is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each nucleoside in a second domain bonded to a 2'-F block in a second domain is independently a 2'-OMe or 2'-MOE modified sugar.

[00215] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-OMe or 2'-MOE modified sugars. In some embodiments, a percentage is about or at least about 30%. In some embodiments, a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%.

In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00216] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-OMe modified sugars. In some embodiments, a percentage is about or at least about 30%. In some embodiments, a percentage is about or at least about 40%. In some embodiments, a percentage is about or at least about 50%. In some embodiments, a percentage is about or at least about 60%. In some embodiments, a percentage is about or at least about 70%. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00217] In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars are 2'-MOE modified sugars.

[00218] In some embodiments, sugars of the first (5'-end) one or several (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, etc.) and/or the last (3'-end) one or several (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, etc.) nucleosides are independently modified sugars. In some embodiments, the first one or several sugars are independently modified sugars. In some embodiments, the last one or several sugars are independently modified sugars. In some embodiments, both the first and last one or several sugars are independently modified sugars. In some embodiments, modified sugars are independently non-2'-F modified sugars, e.g., bicyclic sugars, 2'-OR modified sugars wherein R is as described herein and is not –H (e.g., optionally substituted C_{1-6} aliphatic). In some embodiments, they are independently selected from bicyclic sugars and 2'-OR modified sugars wherein

R is optionally substituted C_{1-6} aliphatic. In some embodiments, they are independently 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, they are independently 2'-OMe modified sugars and 2'-MOE modified sugars. In some embodiments, the first several sugars comprises one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic or bicyclic sugars (e.g., LNA, cEt, etc.) as described herein. In some embodiments, the first several sugars comprises one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the first several sugars comprises one or more 2'-OMe modified sugars. In some embodiments, the first several sugars comprises one or more 2'-MOE modified sugars. In some embodiments, the first several sugars comprises one or more 2'-OMe modified sugars and one or more 2'-MOE modified sugars. In some embodiments, the last several sugars comprises one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic or bicyclic sugars (e.g., LNA, cEt, etc.) as described herein. In some embodiments, the last several sugars comprises one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the last several sugars comprises one or more 2'-OMe modified sugars. In some embodiments, the last several sugars comprises one or more 2'-MOE modified sugars. In some embodiments, the last several sugars comprises one or more 2'-OMe modified sugars and one or more 2'-MOE modified sugars. In some embodiments, the last several sugars are independently 2'-OMe modified sugars. In some embodiments, the first several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive bicyclic sugars or 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the first several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the first several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive modified sugars wherein each modified sugar is independently a 2'-OMe modified sugar or a 2'-MOE modified sugar. In some embodiments, the first several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-OMe modified sugars. In some embodiments, the first several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-MOE modified sugars. In some embodiments, the last several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the last several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive modified sugars wherein each modified sugar is independently a 2'-OMe modified sugar or a 2'-MOE modified sugar. In some embodiments, the last several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-OMe modified sugars. In some embodiments, the last several sugars comprise three or more consecutive 2'-OMe modified sugars. In some embodiments, the last several sugars comprise four or more consecutive 2'-OMe modified sugars. In some embodiments, the last several sugars comprise five or more consecutive 2'-OMe modified sugars. In some embodiments, the last several sugars comprise six or more consecutive 2'-OMe modified sugars. In some embodiments, the last several sugars comprise two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) consecutive 2'-MOE modified sugars.

[00219] In some embodiments, one or more (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of the first several (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars are modified sugars. In some embodiments, one or more (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of the first several (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar (e.g., a sugar comprising 2'−O−CH_2−4', wherein the −CH_2− is optionally substituted (e.g., a LNA sugar, a cET sugar (e.g., (S)-cEt))). In some embodiments, two or more of the first several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, three or more of the first several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, four or more of the first several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the one or more sugars are consecutive. In some embodiments, the first one, two, three or four sugars are modified sugars. In some embodiments, the first two sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the first three sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the first four sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each bicyclic sugar is independently a LNA sugar or a cEt sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the first several sugars, or the first several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the first several sugars, or the first several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the first several sugars, or the first several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OMe modified sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the first several sugars, or the first several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-MOE modified sugar. In some embodiments, the first one, two, three, four or more sugars are independently 2'-OMe modified sugars. In some embodiments, the first sugar is a 2'-OMe modified sugar. In some embodiments, the first two sugars are independently 2'-OMe modified sugars. In some embodiments, the first three sugars are independently 2'-OMe modified sugars. In some embodiments, the first four sugars are independently 2'-OMe modified sugars. In some embodiments, the first one, two, three, four or more sugars are independently 2'-MOE modified sugars. In some embodiments, the first sugar is a 2'-MOE modified sugar. In some embodiments, the first two sugars are independently 2'-MOE modified sugars. In some embodiments, the first three sugars are independently 2'-MOE modified sugars. In some embodiments, the first four sugars are independently 2'-MOE modified sugars. In some embodiments, each

of such modified sugars is independently the sugar of a nucleoside whose nucleobase is optionally substituted or protected A, T, C, G, or U, or an optionally substituted or protected tautomer of A, T, C, G, or U. In some embodiments, one or more such sugars are independently bonded to a non-negatively charged internucleotidic linkage. In some embodiments, one or more such sugars are independently bonded to a neutral internucleotidic linkage such as n001. In some embodiments, a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage, e.g., n001, is chirally controlled. In some embodiments, it is *R*p. In some embodiments, one or more such sugars are independently bonded to a phosphorothioate internucleotidic linkage. In some embodiments, a phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, it is *S*p. In some embodiments, as described herein, the internucleotidic linkage between the first and second nucleosides is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is a phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is chirally controlled. In some embodiments, it is *R*p. In some embodiments, except the internucleotidic linkage between the first and second nucleosides, each internucleotidic linkages bonded to nucleosides comprising the one or more of the first several, or the first several modified sugars are independently phosphorothioate internucleotidic linkages. In some embodiments, each is chirally controlled. In some embodiments, each is *S*p. In some embodiments, a first nucleoside is connected to an additional moiety, e.g., Mod001, optionally through a linker, e.g., L001, through its 5'-end carbon (in some embodiments, via a phosphate group).

[00220] In some embodiments, one or more (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of the last several (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars are modified sugars. In some embodiments, one or more (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of the last several (1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar (e.g., a sugar comprising 2'−O−CH_2−4', wherein the −CH_2− is optionally substituted (e.g., a LNA sugar, a cET sugar (e.g., (S)-cEt))). In some embodiments, two or more of the last several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, three or more of the last several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, four or more of the last several sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the one or more sugars are consecutive. In some embodiments, the last one, two, three or four sugars are modified sugars. In some embodiments, the last two sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the last three sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some embodiments, the last four sugars are modified sugars each independently selected from a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic and a bicyclic sugar. In some

embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each bicyclic sugar is independently a LNA sugar or a cEt sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the last several sugars, or the last several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the last several sugars, or the last several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the last several sugars, or the last several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-OMe modified sugar. In some embodiments, each of the one or more (e.g., 1, 2, 3, 4, or 5) sugars of the last several sugars, or the last several (e.g., 1, 2, 3, 4, or 5) sugar(s), is independently a 2'-MOE modified sugar. In some embodiments, the last one, two, three, four or more sugars are independently 2'-OMe modified sugars. In some embodiments, the last sugar is a 2'-OMe modified sugar. In some embodiments, the last two sugars are independently 2'-OMe modified sugars. In some embodiments, the last three sugars are independently 2'-OMe modified sugars. In some embodiments, the last four sugars are independently 2'-OMe modified sugars. In some embodiments, the last one, two, three, four or more sugars are independently 2'-MOE modified sugars. In some embodiments, the last sugar is a 2'-MOE modified sugar. In some embodiments, the last two sugars are independently 2'-MOE modified sugars. In some embodiments, the last three sugars are independently 2'-MOE modified sugars. In some embodiments, the last four sugars are independently 2'-MOE modified sugars. In some embodiments, each of such modified sugars is independently the sugar of a nucleoside whose nucleobase is optionally substituted or protected A, T, C, G, or U, or an optionally substituted or protected tautomer of A, T, C, G, or U. In some embodiments, one or more such sugars are independently bonded to a non-negatively charged internucleotidic linkage. In some embodiments, one or more such sugars are independently bonded to a neutral internucleotidic linkage such as n001. In some embodiments, a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage, e.g., n001, is chirally controlled. In some embodiments, it is *R*p. In some embodiments, one or more such sugars are independently bonded to a phosphorothioate internucleotidic linkage. In some embodiments, a phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, it is *S*p. In some embodiments, as described herein, the internucleotidic linkage between the last and second last nucleosides is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is a phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is chirally controlled. In some embodiments, it is *R*p. In some embodiments, except the internucleotidic linkage between the last and second last nucleosides, each internucleotidic linkages bonded to nucleosides comprising the one or more of the last several, or the last several modified sugars are independently phosphorothioate internucleotidic linkages. In some embodiments, each is chirally controlled. In some embodiments, each is *S*p.

[00221] In some embodiments, a sugar at position +1 is a 2'-F modified sugar. In some embodiments, a sugar at position +1 is a natural DNA sugar. In some embodiments, a sugar at position 0 is a natural DNA

sugar (nucleoside at position 0 is opposite to a target adenosine when aligned). In some embodiments, a sugar at position -1 is a DNA sugar. In some embodiments, a sugar at position -2 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar (e.g., a sugar comprising 2'−O−CH_2−4', wherein the −CH_2− is optionally substituted (e.g., a LNA sugar, a cET sugar (e.g., (S)-cEt))). In some embodiments, it is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, it is a 2'-OMe modified sugar. In some embodiments, it is a 2'-MOE modified sugar. In some embodiments, it is a bicyclic sugar. In some embodiments, it is a LNA sugar. In some embodiments, it is a cEt sugar. In some embodiments, a sugar at position -3 is a 2'-F modified sugar. In some embodiments, each sugar after position -3 (e.g., position -4, -5, -6, etc.) is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar (e.g., a sugar comprising 2'−O−CH_2−4', wherein the −CH_2− is optionally substituted (e.g., a LNA sugar, a cET sugar (e.g., (S)-cEt))). In some embodiments, each is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each is a 2'-OMe modified sugar. In some embodiments, each is a 2'-MOE modified sugar. In some embodiments, one or more are independently 2'-OMe modified sugars, and one or more are independently 2'-MOE modified sugars. In some embodiments, as described herein, the internucleotidic linkage between nucleosides at positions -1 and-2 is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is a phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is chirally controlled. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, the internucleotidic linkage between nucleosides at positions -2 and -3 is a natural phosphate linkage. In some embodiments, as described herein, the internucleotidic linkage between the last and second last nucleosides is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is a phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is chirally controlled. In some embodiments, it is *R*p. In some embodiments, each internucleotidic linkages between nucleosides to the 3'-side of a nucleoside opposite to a target adenosine, except those between nucleosides at positions -1 and -2, and between nucleosides at positions -2 and -3, and between the last and the second last nucleosides, is independently a phosphorothioate internucleotidic linkages. In some embodiments, each phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, each is *S*p.

[00222] In some embodiments, the first and/or last one or several sugars are modified sugars, e.g., bicyclic sugars and/or 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe modified sugars, 2'-MOE modified sugars, etc.). In some embodiments, such sugars may increase stability, affinity and/or activity of an oligonucleotide. In some embodiments, when conjugated to one or more additional chemical moieties, sugars at 5'- and/or 3'-ends of oligonucleotides are not bicyclic sugars or 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 5'-end sugar is a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments,

such a 5'-end sugar is not connected to an additional chemical moiety. In some embodiments, a 5'-end sugar is a 2'-F modified sugar. In some embodiments, a 5'-end sugar is a 2'-F modified sugar conjugated to an additional chemical moiety. In some embodiments, a 3'-end sugar is a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, such a 3'-end sugar is not connected to an additional chemical moiety. In some embodiments, a 3'-end sugar is a 2'-F modified sugar. In some embodiments, a 3'-end sugar is a 2'-F modified sugar conjugated to an additional chemical moiety. In some embodiments, the last several sugars are 3'-side sugars relative to a nucleoside opposite to a target adenosine (e.g., sugars of 3'-side nucleosides such as N_{-1}, N_{-2}, etc.). In some embodiments, the last several sugars or the 3'-side sugars comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-F modified sugars. In some embodiments, the last several sugars or the 3'-side sugars comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) consecutive 2'-F modified sugars. In some embodiments, the last several sugars or the 3'-side sugars comprises one or more, or two or more consecutive, 2'-F modified sugars, and sugar of the last nucleoside of an oligonucleotide is a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, as described herein a 2'-OR modified sugar is a 2'-OMe modified sugar or a 2'-MOE modified sugar; in some embodiments, it is a 2'-OMe modified sugar; in some embodiments, it is a 2'-MOE modified sugar. In some embodiments, the last several sugars or the 3'-side sugars comprises one or more, or two or more consecutive, 2'-F modified sugars, and sugar of the last nucleoside of an oligonucleotide is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, the last several sugars or the 3'-side sugars comprises one or more, or two or more consecutive, 2'-F modified sugars, and sugar of the last nucleoside of an oligonucleotide is a 2'-OMe modified sugar or a 2'-MOE modified sugar. In some embodiments, the last several sugars or the 3'-side sugars comprises one or more, or two or more consecutive, 2'-F modified sugars, and sugar of the last nucleoside of an oligonucleotide is a 2'-OMe modified sugar. In some embodiments, the last several sugars or the 3'-side sugars comprises one or more, or two or more consecutive, 2'-F modified sugars, and sugar of the last nucleoside of an oligonucleotide is a 2'-MOE modified sugar. In some embodiments, two and no more than two nucleosides at the 3'-side of a nucleoside opposite to an adenosine independently have a 2'-F modified sugar. In some embodiments, they are at positions -4 and -5. In some embodiments, they are the second and third last nucleosides of an oligonucleotide. In some embodiments, one and no more than one nucleoside at the 3'-side of a nucleoside opposite to an adenosine has a 2'-F modified sugar. In some embodiments, it is at position -3. In some embodiments, it is 4th last nucleoside of an oligonucleotide.

[00223] In some embodiments, a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic is present in a region which comprises one or more (e.g., 1-30, 1-25, 1-20, 1-15, 1-10, 2-30, 2-25, 2-20, 2-25, 2-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) sugars are 2'-F modified. In some embodiments, a majority of sugars as described herein in such a region are 2'-F modified sugars. In some embodiments, two or more 2'-F modified sugars are consecutive. In some embodiments, a region is a first domain. In some embodiments, a bicyclic sugar is present in such a region.

In some embodiments, a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic is present in such a region. In some embodiments, a 2'-OMe modified sugar is present in such a region. In some embodiments, a 2'-MOE modified sugar is present in such a region.

[00224] In some embodiments, one or more sugars at positions -5, -4, -3, +1, +2, +4, +5, +6, +7, and +8 (position 0 being the position of a nucleoside opposite to a target adenosine; "+" is going from a nucleoside opposite to a target adenosine toward 5'-end of an oligonucleotide, and "-" is going from a nucleoside opposite to a target adenosine toward 3'-end of an oligonucleotide; for example, in 5'-$N_1N_0N_{-1}$-3', if N_0 is a nucleoside opposite to a target adenosine, it is at position 0, and N_1 is at position +1 and N_{-1} is at position -1) are independently 2'-F modified sugars. In some embodiments, a sugar at position +1, and one or more sugars at positions -5, -4, -3, +2, +4, +5, +6, +7, and +8, are independently 2'-F modified sugars. In some embodiments, a sugar at position +1, and one sugar at position -5, -4, -3, +2, +4, +5, +6, +7, and +8, are independently 2'-F modified sugars.

[00225] In some embodiments, an oligonucleotide comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, 2-10, 3-10, 2-5, 2-4, 2-3, 3-5, 3-4, etc.) natural DNA sugars. In some embodiments, one or more natural DNA sugars are at an editing region, e.g., positions +1, 0, and/or -1. In some embodiments, a natural DNA sugar is within the first several nucleosides of an oligonucleotides (e.g., the first 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides). In some embodiments, the first, second, and/or third nucleosides of an oligonucleotides independently have a natural DNA sugar. In some embodiments, a natural DNA sugar is bonded to a modified internucleotidic linkage such as a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, a phosphoryl guanidine internucleotidic linkage, n001, or a phosphorothioate internucleotidic linkage (in various embodiments, *S*p).

[00226] Oligonucleotides may contain various types of internucleotidic linkages. In some embodiments, oligonucleotides comprises one or more modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is n001. In some embodiments, oligonucleotides comprises one or more natural phosphate linkages. In some embodiments, a natural phosphate linkage bonds to a nucleoside comprising a modified sugar that can improve stability (e.g., resistance toward nuclease). In some embodiments, a natural phosphate linkage bonds to a bicyclic sugar. In some embodiments, a natural phosphate linkage bonds to a 2'-modified sugar. In some embodiments, a natural phosphate linkage bonds to a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a natural phosphate linkage bonds to a 2'-OMe modified sugar. In some embodiments, a natural phosphate linkage bonds to a 2'-MOE modified sugar. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, a non-

negatively charged internucleotidic linkage, and a natural phosphate linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, a neutral internucleotidic linkage, and a natural phosphate linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, a phosphoryl guanidine internucleotidic linkage, and a natural phosphate linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, n001, and a natural phosphate linkage. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled. In some embodiments, one or more chiral internucleotidic linkage is not chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled. In some embodiments, a majority or each phosphorothioate internucleotidic linkage is *Sp* as described herein. In some embodiments, a majority or each non-negatively charged internucleotidic linkage, e.g., n001, is *Rp*. In some embodiments, a majority or each non-negatively charged internucleotidic linkage, e.g., n001, is *Sp*.

[00227] In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage and a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage and a neutral internucleotidic linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage and a phosphoryl guanidine internucleotidic linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage and n001. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled. In some embodiments, one or more chiral internucleotidic linkage is not chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, each chiral internucleotidic linkage is independently chirally controlled. In some embodiments, a majority or each phosphorothioate internucleotidic linkage is *Sp* as described herein. In some embodiments, one or more (e.g., 1, 2, 3, 4, or 5) phosphorothioate internucleotidic linkages are *Rp*. In some embodiments, a majority or each non-negatively charged internucleotidic linkage, e.g., n001, is *Rp*. In some embodiments, a majority or each non-negatively charged internucleotidic linkage, e.g., n001, is *Sp*. In some embodiments, an oligonucleotide comprises no natural phosphate linkages. In some embodiments, each internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage. In some embodiments, each internucleotidic linkage is independently a phosphorothioate or a neutral charged internucleotidic linkage. In some embodiments, each internucleotidic linkage is independently a phosphorothioate or phosphoryl guanidine internucleotidic linkages. In some embodiments, each internucleotidic linkage is independently a phosphorothioate or n001 internucleotidic linkage. In some embodiments, the last internucleotidic linkage of an oligonucleotide is a non-negatively charged internucleotidic linkage, or is a neutral internucleotidic linkage, or is a phosphoryl guanidine internucleotidic linkage, or is n001.

[00228] In some embodiments, oligonucleotides of the present disclosure comprise one or more modified nucleobases. Various modifications can be introduced to a sugar and/or nucleobase in accordance with the

present disclosure. For example, in some embodiments, a modification is a modification described in US 9006198. In some embodiments, a modification is a modification described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the sugars, bases, and internucleotidic linkages of each of which are independently incorporated herein by reference.

[00229] In some embodiments, a nucleobase in a nucleoside is or comprises Ring BA which has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

[00230] In some embodiments, a sugar is a modified sugar comprising a 2'-modificatin, e.g., 2'-F, 2'-OR wherein R is optionally substituted aliphatic, or a bicyclic sugar (e.g., a LNA sugar), or a acyclic sugar (e.g., a UNA sugar).

[00231] In some embodiments, as described herein, provided oligonucleotides comprise one or more domains, each of which independently has certain lengths, modifications, linkage phosphorus stereochemistry, etc., as described herein. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more modified sugars and/or one or more modified internucleotidic linkages, wherein the oligonucleotide comprises a first domain and a second domain each independently comprising one or more nucleobases. In some embodiments, the present disclosure provides oligonucleotide comprising one or more domains and/or subdomains as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising a first domain as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising a second domain as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising a first subdomain as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising a second subdomain as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising a third subdomain as described herein. In some embodiments, the present disclosure provides oligonucleotides comprising one or more regions each independently selected from a first domain, a second domain, a first subdomain, a second subdomain and a third subdomain, each of which is independently as described herein. In some embodiments, the present disclosure provides an oligonucleotide comprising:

a first domain; and

a second domain,

wherein:

the first domain comprises one or more 2'-F modifications;

the second domain comprises one or more sugars that do not have a 2'-F modification.

[00232] In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar is a bicyclic sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar). In some embodiments, a modified sugar comprises a 5'-modification. Typically, oligonucleotides of the present disclosure have a free 5'-OH at its 5'-end and a free 3'-OH at its 3'-end unless indicated otherwise, e.g., by context. In some embodiments, a 5'-end sugar of an oligonucleotide may comprise a modified 5'-OH.

[00233] In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all sugars in an oligonucleotide or a portion thereof, respectively. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%.

[00234] In some embodiments, a majority is at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In some embodiments, a majority is about 50%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, a majority is about or at least about 50%. In some embodiments, a majority is about or at least about 55%. In some embodiments, a majority is about or at least about 60%. In some embodiments, a majority is about or at least about 65%. In some embodiments, a majority is about or at least about 70%. In some embodiments, a majority is about or at least about 75%. In some embodiments, a majority is about or at least about 80%. In some embodiments, a majority is about or at least about 85%. In some embodiments, a majority is about or at least about 90%. In some embodiments, a majority is about or at least about 95%.

[00235] In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of modified internucleotidic linkages. In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain,

a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of chiral internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%.

[00236] In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of chirally controlled internucleotidic linkages. In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of *Sp* internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about

95%. In some embodiments, a percentage is about 100%.

[00237] In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of *S*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, about 1-50, 1-40, 1-30, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *S*p chiral internucleotidic linkages. In many embodiments, it was observed that a high percentage (e.g., relative to *R*p internucleotidic linkages and/or natural phosphate linkages) of *S*p internucleotidic linkages in an oligonucleotide or certain portions thereof can provide improved properties and/or activities, e.g., high stability and/or high adenosine editing activity.

[00238] In some embodiments, an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.) comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-

100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in an oligonucleotide or a portion thereof, respectively. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, about 1-50, 1-40, 1-30, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *R*p chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about 4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is

about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10.

[00239] While not wishing to be bound by theory, it is noted that in some instances *R*p and *S*p configurations of internucleotidic linkages may affect structural changes in helical conformations of double stranded complexes formed by oligonucleotides and target nucleic acids such as RNA, and ADAR proteins may recognize and interact various targets (e.g., double stranded complexes formed by oligonucleotides and target nucleic acids such as RNA) through multiple domains. In some embodiments, provided oligonucleotides and compositions thereof promote and/or enhance interaction profiles of oligonucleotide, target nucleic acids, and/or ADAR proteins to provide efficient adenosine modification by ADAR proteins through incorporation of various modifications and/or control of stereochemistry.

[00240] In some embodiments, an oligonucleotide can have or comprise a base sequence; internucleotidic linkage, base modification, sugar modification, additional chemical moiety, or pattern thereof; and/or any other structural element described herein, e.g., in Tables.

[00241] In some embodiments, a provided oligonucleotide or composition is characterized in that, when it is contacted with a target nucleic acid comprising a target adenosine in a system (e.g., an ADAR-mediated deamination system), modification of the target adenosine (e.g., deamination of the target A) is improved relative to that observed under reference conditions (e.g., selected from the group consisting of absence of the composition, presence of a reference oligonucleotide or composition, and combinations thereof). In some embodiments, modification, e.g., ADAR-mediated deamination (e.g., endogenous ADAR-meidated deamination) is increased 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 fold or more.

[00242] In some embodiments, oligonucleotides are provided as salt forms. In some embodiments, oligonucleotides are provided as salts comprising negatively-charged internucleotidic linkages (e.g., phosphorothioate internucleotidic linkages, natural phosphate linkages, etc.) existing as their salt forms. In some embodiments, oligonucleotides are provided as pharmaceutically acceptable salts. In some embodiments, oligonucleotides are provided as metal salts. In some embodiments, oligonucleotides are provided as sodium salts. In some embodiments, oligonucleotides are provided as ammonium salts. In some embodiments, oligonucleotides are provided as metal salts, e.g., sodium salts, wherein each negatively-charged internucleotidic linkage is independently in a salt form (e.g., for sodium salts, −O−P(O)(SNa)−O− for a phosphorothioate internucleotidic linkage, −O−P(O)(ONa)−O− for a natural phosphate linkage, etc.).

[00243] In some embodiments, oligonucleotides are chiral controlled, comprising one or more chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotides are stereochemically pure. In some embodiments, provided oligonucleotides or compositions thereof are substantially pure of other stereoisomers. In some embodiments, the present disclosure provides chirally controlled oligonucleotide

compositions.

[00244] As described herein, oligonucleotides of the present disclosure can be provided in high purity (e.g., 50%-100%). In some embodiments, oligonucleotides of the present disclosure are of high stereochemical purity (e.g., 50%-100%). In some embodiments, oligonucleotides in provided compositions are of high stereochemical purity (e.g., high percentage (e.g., 50%-100%) of a stereoisomer compared to the other stereoisomers of the same oligonucleotide). In some embodiments, a percentage is at least or about 50%. In some embodiments, a percentage is at least or about 60%. In some embodiments, a percentage is at least or about 70%. In some embodiments, a percentage is at least or about 75%. In some embodiments, a percentage is at least or about 80%. In some embodiments, a percentage is at least or about 85%. In some embodiments, a percentage is at least or about 90%. In some embodiments, a percentage is at least or about 95%.

First Domains

[00245] As described herein, in some embodiment, an oligonucleotide comprises a first domain and a second domain. In some embodiments, an oligonucleotide consists of a first domain and a second domain. Certain embodiments are described below as examples.

[00246] In some embodiments, a first domain has a length of about 2-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases. In some embodiments, a first domain has a length of about 5-30 nucleobases. In some embodiments, a first domain has a length of about 10-30 nucleobases. In some embodiments, a first domain has a length of about 10-20 nucleobases. In some embodiments, a first domain has a length of about 13-16 nucleobases. In some embodiments, a first domain has a length of 10 nucleobases. In some embodiments, a first domain has a length of 11 nucleobases. In some embodiments, a first domain has a length of 12 nucleobases. In some embodiments, a first domain has a length of 13 nucleobases. In some embodiments, a first domain has a length of 14 nucleobases. In some embodiments, a first domain has a length of 15 nucleobases. In some embodiments, a first domain has a length of 16 nucleobases. In some embodiments, a first domain has a length of 17 nucleobases. In some embodiments, a first domain has a length of 18 nucleobases. In some embodiments, a first domain has a length of 19 nucleobases. In some embodiments, a first domain has a length of 20 nucleobases.

[00247] In some embodiments, a first domain is about, or at least about, 5-95%, 10%-90%, 20%-80%, 30%-70%, 40%-70%, 40%-60%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% of an oligonucleotide. In some embodiments, a percentage is about 30%-80%. In some embodiments, a percentage is about 30%-70%. In some embodiments, a percentage is about 40%-60%. In some embodiments, a percentage is about 20%. In some embodiments, a percentage is about 25%. In some embodiments, a percentage is about 30%. In some embodiments, a percentage is about 35%. In some embodiments, a percentage is about 40%. In some embodiments, a percentage is about 45%. In some embodiments, a percentage is about 50%. In some embodiments, a percentage is about 55%. In some

embodiments, a percentage is about 60%. In some embodiments, a percentage is about 65%. In some embodiments, a percentage is about 70%. In some embodiments, a percentage is about 75%. In some embodiments, a percentage is about 80%. In some embodiments, a percentage is about 85%. In some embodiments, a percentage is about 90%.

[00248] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches exist in a first domain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches.

[00249] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles exist in a first domain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 wobble. In some embodiments, there are 2 wobbles. In some embodiments, there are 3 wobbles. In some embodiments, there are 4 wobbles. In some embodiments, there are 5 wobbles. In some embodiments, there are 6 wobbles. In some embodiments, there are 7 wobbles. In some embodiments, there are 8 wobbles. In some embodiments, there are 9 wobbles. In some embodiments, there are 10 wobbles.

[00250] In some embodiments, duplexes of oligonucleotides and target nucleic acids in a first domain region comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

[00251] In some embodiments, a first domain is fully complementary to a target nucleic acid.

[00252] In some embodiments, a first domain comprises one or more modified nucleobases.

[00253] In some embodiments, a second domain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars). In some embodiments, a second domain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a first domain comprises one or more modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar is a bicyclic sugar, e.g., a LNA sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar).

[00254] In some embodiments, a first domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars. In some embodiments, a first domain comprises about 1-50

(e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars with 2'-F modification. In some embodiments, a first domain comprises about 2-50 (e.g., about 2, 3, 4, 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., 2-40, 2-30, 2-25, 2-20, 2-15, 2-10, 3-40, 3-30, 3-25, 3-20, 3-15, 3-10, 4-40, 4-30, 4-25, 4-20, 4-15, 4-10, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 6-40, 6-30, 6-25, 6-20, 6-15, 6-10, 7-40, 7-30, 7-25, 7-20, 7-15, 7-10, 8-40, 8-30, 8-25, 8-20, 8-15, 8-10, 9-40, 9-30, 9-25, 9-20, 9-15, 9-10, 10-40, 10-30, 10-25, 10-20, 10-15, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) consecutive modified sugars with 2'-F modification. In some embodiments, a first domain comprises 2 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 3 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 4 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 5 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 6 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 7 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 8 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 9 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises 10 consecutive 2'-F modified sugars. In some embodiments, a first domain comprises two or more 2'-F modified sugar blocks, wherein each sugar in a 2'-F modified sugar block is independently a 2'-F modified sugar. In some embodiments, each 2'-F modified sugar block independently comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive 2'-F modified sugars as described herein. In some embodiments, two consecutive 2'-F modified sugar blocks are independently separated by a separating block which separating block comprises one or more sugars that are independently not 2'-F modified sugars. In some embodiments, each sugar in a separating block is independently not 2'-F modified. In some embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) or all sugars in a separating block are independently not 2'-F modified. In some embodiments, a separating block comprises one or more bicyclic sugars (e.g., LNA sugar, cEt sugar, etc.) and/or one or more 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, a separating block comprises one or more 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, two or more non-2'-F modified sugars are consecutive. In some embodiments, two or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.) are consecutive. In some embodiments, a separating block comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, a separating block comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) consecutive 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe, 2'-MOE, etc.). In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe sugar. In some

embodiments, each 2'-OR modified sugar is independently a 2'-MOE sugar. In some embodiments, a separating block comprises one or more 2'-F modified sugars. In some embodiments, none of 2'-F modified sugars in a separating block are next to each other. In some embodiments, a separating block contain no 2'-F modified sugars. In some embodiments, each sugar in a separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each sugar in each separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each sugar in a separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in each separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a separating block is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in each separating block is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in a separating block is independently a 2'-OMe modified sugar. In some embodiments, each sugar in a separating block is independently a 2'-MOE modified sugar. In some embodiments, a separating block comprises a 2'-OMe sugar and 2'-MOE modified sugar. In some embodiments, each 2'-F block and each separating block independently contains 1, 2, 3, 4, or 5 nucleosides. In some embodiments, each 2'-F block and each separating block independently contains 1, 2, or 3 nucleosides.

[00255] In some embodiments, about 5%-100%, (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a first domain are independently a modified sugar. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a first domain are independently a 2'-F modified sugar. In some embodiments, a percentage is at least about 40%. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 60%. In some embodiments, a percentage is about or no more than about 70%. In some embodiments, a

percentage is about or no more than about 80%. In some embodiments, a percentage is about or no more than about 90%.

[00256] In some embodiments, a first domain comprises no bicyclic sugars or 2'-OR modified sugars wherein R is not –H. In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H. In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-OR modified sugars wherein R is not –H. In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-OR modified sugars wherein R is optionally substituted C_{1-10} aliphatic. In some embodiments, levels of bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H, individually or combined, are relatively low compared to level of 2'-F modified sugars. In some embodiments, levels of bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H, individually or combined, are about 10%–80% (e.g., about 10%-75%, 10-70%, 10%-65%, 10%-60%, 10%-50%, about 20%-60%, about 30%-60%, about 20%-50%, about 30%-50%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60%, etc.). In some embodiments, levels of 2'-OR modified sugars wherein R is not –H combined (e.g., 2'-OMe and 2'-MOE modified sugars combined, if any) are about 10–70% (e.g., about 10%-60%, 10%-50%, about 20%-60%, about 30%-60%, about 20%-50%, about 30-50%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60%, etc.). In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a first domain comprises 2'-OMe. In some embodiments, no more than about 50% of sugars in a first domain comprises 2'-OMe. In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 50% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 40% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 30% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 25% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 20% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, no more than about 10% of sugars in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, as described herein, 2'-OR is 2'-MOE. In some embodiments, as described herein, 2'-OR is 2'-MOE or 2'-OMe. In some embodiments, a first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification. In some embodiments, a first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification. In some embodiments, a first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) bicyclic sugars,

e.g., LNA sugars. In some embodiments, a first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars). In some embodiments, a number of 5'-end sugars in a first domain are independently 2'-OR modified sugars, wherein R is not −H. In some embodiments, a number of (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 5'-end sugars in a first domain are independently 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, the first about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, sugars from the 5'-end of a first domain are independently 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, the first one is 2'-OR modified. In some embodiments, the first two are independently 2'-OR modified. In some embodiments, the first three are independently 2'-OR modified. In some embodiments, the first four are independently 2'-OR modified. In some embodiments, the first five are independently 2'-OR modified. In some embodiments, all 2'-OR modification in a domain (e.g., a first domain), a subdomain (e.g., a first subdomain), or an oligonucleotide are the same. In some embodiments, 2'-OR is 2'-MOE. In some embodiments, 2'-OR is 2'-OMe.

[00257] In some embodiments, no sugar in a first domain comprises 2'-OR. In some embodiments, no sugar in a first domain comprises 2'-OMe. In some embodiments, no sugar in a first domain comprises 2'-MOE. In some embodiments, no sugar in a first domain comprises 2'-MOE or 2'-OMe. In some embodiments, no sugar in a first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a first domain comprises 2'-F.

[00258] In some embodiments, about 40-70% (e.g., about 40%-70%, 40%-60%, 50%-70%, 50%-60%, etc., or about 40%, 45%, 50%, 55%, 60%, 65%, 70%, etc.) of sugars in a first domain are 2'-F modified, and about 10%-60% (e.g., about 10%-50%, 20%-60%, 30%-60%, 30%-50%, 40%-50%, etc., or about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60%) of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars (e.g., LNA sugars, cEt sugars, etc.). In some embodiments, about 20%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 25%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 30%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 35%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 40%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 50%-60% of sugars in a first domain are 2'-F modified. In some embodiments, about 50%-70% of sugars in a first domain are 2'-F modified. In some embodiments, about 20%-60% of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars. In some embodiments, about 30%-60% of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars. In some embodiments, about 40%-60% of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars. In some embodiments, about 30%-50% of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars. In some embodiments, about 40%-50% of sugars in a first domain are independently 2'-OR modified wherein R is not −H or bicyclic sugars. In some embodiments, each of the sugars in a first domain that are independently 2'-OR modified wherein R is

not −H or bicyclic sugars is independently a 2'-OR modified sugar wherein R is not −H. In some embodiments, each of them is independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, each of them is independently a 2'-OR modified sugar wherein R is C_{1-6} alky. In some embodiments, each of them is independently a 2'-OMe or 2'-MOE modified sugar.

[00259] In some embodiments, a first domain comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in a first domain are modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a first domain is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a neutral internucleotidic linkage, e.g., n001. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a first domain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a first domain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-

80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a first domain is chirally controlled. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a first domain is *S*p. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) phosphorothioate internucleotidic linkages in a first domain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a first domain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a first domain is *S*p. In some embodiments, the number is one or more. In some embodiments, the number is 2 or more. In some embodiments, the number is 3 or more. In some embodiments, the number is 4 or more. In some embodiments, the number is 5 or more. In some embodiments, the number is 6 or more. In some embodiments, the number is 7 or more. In some embodiments, the number is 8 or more. In some embodiments, the number is 9 or more. In some embodiments, the number is 10 or more. In some embodiments, the number is 11 or more. In some embodiments, the number is 12 or more. In some embodiments, the number is 13 or more. In some embodiments, the number is 14 or more. In some embodiments, the number is 15 or more. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, each internucleotidic linkages linking two first domain

nucleosides is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage is independently a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *Sp* chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *Sp* phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkages is independently a *Sp* phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage of a first domain is bonded to two nucleosides of the first domain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a first domain and a nucleoside in a second domain may be properly considered an internucleotidic linkage of a first domain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a first domain and a nucleoside in a second domain is a modified internucleotidic linkage; in some embodiments, it is a chiral internucleotidic linkage; in some embodiments, it is chirally controlled; in some embodiments, it is *R*p; in some embodiments, it is *S*p. In many embodiments, it was observed that a high percentage (e.g., relative to *R*p internucleotidic linkages and/or natural phosphate linkages) of *S*p internucleotidic linkages provide improved properties and/or activities, e.g., high stability and/or high adenosine editing activity.

[00260] In some embodiments, a first domain comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in a first domain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in a first domain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in a first domain. In some embodiments, a percentage is about

or no more than about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 1-5, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *R*p chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about 4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10.

[00261] In some embodiments, each phosphorothioate internucleotidic linkage in a first domain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a first domain is chirally controlled and is *S*p.

[00262] In some embodiments, as illustrated in certain examples, a first domain comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in a first domain is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, it is about 1. In

some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in a first domain are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more consecutive non-negatively charged internucleotidic linkages, are at the 5'-end of a first domain. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first domain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first domain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first domain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first domain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first domain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first domain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first domain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first domain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first domain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first domain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage such as n001. In some embodiments, the first two nucleosides of a first domain are the first two nucleosides of an oligonucleotide.

[00263] In some embodiments, a first domain comprises one or more natural phosphate linkages. In some embodiments, a first domain contains no natural phosphate linkages. In some embodiments, one or more 2'-OR modified sugars wherein R is not −H are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-OMe modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-MOE modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, each 2'-MOE modified sugar is independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-OR modified sugars wherein R is not −H are independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-OMe modified sugars are independently bonded to a natural phosphate linkage. In some

embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-MOE modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) internucleotidic linkages bonded to two 2'-OR modified sugars are independently natural phosphate linkages. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) internucleotidic linkages bonded to two 2'-OMe or 2'-MOE modified sugars are independently natural phosphate linkages.

[00264] In some embodiments, in an oligonucleotide of the present disclosure or a portion thereof, e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc., each internucleotidic linkage bonded to two 2'-F modified sugars is independently a modified internucleotidic linkage. In some embodiments, it is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage such as a phosphoryl guanidine internucleotidic linkage like n001. In some embodiments, it is independently a *Sp* phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage such as a phosphoryl guanidine internucleotidic linkage like n001. In some embodiments, it is independently a *Sp* phosphorothioate internucleotidic linkage or a *Rp* phosphoryl guanidine internucleotidic linkage like *Rp* n001. In some embodiments, each phosphorothioate internucleotidic linkage bonded to two 2'-F modified sugars is independently *Sp*.

[00265] In some embodiments, a first domain recruits, promotes or contribute to recruitment of, a protein such as an ADAR protein (e.g., ADAR1, ADAR2, etc.). In some embodiments, a first domain recruits, or promotes or contribute to interactions with, a protein such as an ADAR protein. In some embodiments, a first domain contacts with a RNA binding domain (RBD) of ADAR. In some embodiments, a first domain does not substantially contact with a second RBD domain of ADAR. In some embodiments, a first domain does not substantially contact with a catalytic domain of ADAR which has a deaminase activity. In some embodiments, various nucleobases, sugars and/or internucleotidic linkages may interact with one or more residues of proteins, e.g., ADAR proteins.

Second Domains

[00266] As described herein, in some embodiment, an oligonucleotide comprises a first domain and a second domain from 5' to 3'. In some embodiments, an oligonucleotide consists of a first domain and a second domain. Certain embodiments of a second domain are described below as examples. In some embodiments, a second domain comprise a nucleoside opposite to a target adenosine to be modified (e.g., conversion to I).

[00267] In some embodiments, a second domain has a length of about 2-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases. In some embodiments, a second domain has a length of about 5-30 nucleobases. In some embodiments, a second domain has a length of about 10-30 nucleobases. In some embodiments, a second domain has a length of about 10-20 nucleobases.

In some embodiments, a second domain has a length of about 5-15 nucleobases. In some embodiments, a second domain has a length of about 13-16 nucleobases. In some embodiments, a second domain has a length of about 1-7 nucleobases. In some embodiments, a second domain has a length of 10 nucleobases. In some embodiments, a second domain has a length of 11 nucleobases. In some embodiments, a second domain has a length of 12 nucleobases. In some embodiments, a second domain has a length of 13 nucleobases. In some embodiments, a second domain has a length of 14 nucleobases. In some embodiments, a second domain has a length of 15 nucleobases. In some embodiments, a second domain has a length of 16 nucleobases. In some embodiments, a second domain has a length of 17 nucleobases. In some embodiments, a second domain has a length of 18 nucleobases. In some embodiments, a second domain has a length of 19 nucleobases. In some embodiments, a second domain has a length of 20 nucleobases.

[00268] In some embodiments, a second domain is about, or at least about, 5-95%, 10%-90%, 20%-80%, 30%-70%, 40%-70%, 40%-60%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% of an oligonucleotide. In some embodiments, a percentage is about 30%-80%. In some embodiments, a percentage is about 30%-70%. In some embodiments, a percentage is about 40%-60%. In some embodiments, a percentage is about 20%. In some embodiments, a percentage is about 25%. In some embodiments, a percentage is about 30%. In some embodiments, a percentage is about 35%. In some embodiments, a percentage is about 40%. In some embodiments, a percentage is about 45%. In some embodiments, a percentage is about 50%. In some embodiments, a percentage is about 55%. In some embodiments, a percentage is about 60%. In some embodiments, a percentage is about 65%. In some embodiments, a percentage is about 70%. In some embodiments, a percentage is about 75%. In some embodiments, a percentage is about 80%. In some embodiments, a percentage is about 85%. In some embodiments, a percentage is about 90%.

[00269] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches exist in a second domain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches.

[00270] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles exist in a second domain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 wobble. In some embodiments, there are 2 wobbles. In some embodiments, there are 3 wobbles. In some embodiments, there are 4 wobbles. In some embodiments, there are 5 wobbles. In some embodiments, there are 6 wobbles. In some embodiments, there are 7 wobbles. In some embodiments, there are 8 wobbles. In some embodiments, there are 9 wobbles. In some embodiments, there are 10 wobbles.

[00271] In some embodiments, duplexes of oligonucleotides and target nucleic acids in a second domain

region comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

[00272] In some embodiments, a second domain is fully complementary to a target nucleic acid.

[00273] In some embodiments, a second domain comprises one or more modified nucleobases.

[00274] In some embodiments, a second domain comprise a nucleoside opposite to a target adenosine, e.g., when the oligonucleotide forms a duplex with a target nucleic acid. In some embodiments, an opposite nucleobase is optionally substituted or protected U, or is an optionally substituted or protected tautomer of U. In some embodiments, an opposite nucleobase is U.

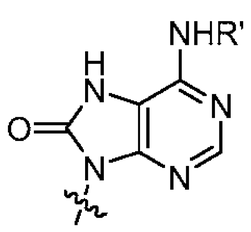
[00275] In some embodiments, an opposite nucleobase has weaker hydrogen bonding with a target adenine of a target adenosine compared to U. In some embodiments, an opposite nucleobase forms fewer hydrogen bonds with a target adenine of a target adenosine compared to U. In some embodiments, an opposite nucleobase forms one or more hydrogen bonds with one or more amino acid residues of a protein, e.g., ADAR, which residues form one or more hydrogen bonds with U opposite to a target adenosine. In some embodiments, an opposite nucleobase forms one or more hydrogen bonds with each amino acid residue of ADAR that forms one or more hydrogen bonds with U opposite to a target adenosine. In some embodiments, by weakening hydrogen boding with a target A and/or maintaining or enhancing interactions with proteins such as ADAR1, ADAR2, etc., certain opposite nucleobase facilitate and/or promote adenosine modification, e.g., by ADAR proteins such as ADAR1 and ADAR2.

[00276] In some embodiments, an opposite nucleobase is optionally substituted or protected C, or is an optionally substituted or protected tautomer of C. In some embodiments, an opposite nucleobase is C. In some embodiments, an opposite nucleobase is optionally substituted or protected A, or is an optionally substituted or protected tautomer of A. In some embodiments, an opposite nucleobase is A. In some embodiments, an opposite nucleobase is optionally substituted or protected nucleobase of pseudoisocytosine, or is an optionally substituted or protected tautomer of the nucleobase of pseudoisocytosine. In some embodiments, an opposite nucleobase is the nucleobase of pseudoisocytosine.

[00277] In some embodiments, a nucleoside, e.g., a nucleoside opposite to a target adenosine (may also be referred to as "an opposite nucleoside") is abasic as described herein (e.g., having the structure of L010, L012, L028, etc.).

[00278] Many useful embodiments of modified nucleobases, e.g., for opposite nucleobases, are also described below. In some embodiments, as described herein (e.g., in various oligonucleotides), the present disclosure provides oligonucleotides comprising a nucleobase, e.g., of a nucleoside opposite to a target nucleoside such as A, which is or comprises A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U,

b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, and zdnp. In some embodiments, as described herein (e.g., in various oligonucleotides), the present disclosure provides oligonucleotides comprising a nucleobase, e.g., of a nucleoside opposite to a target nucleoside such as A, which is or comprises b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, and zdnp. In some embodiments, as described herein (e.g., in various oligonucleotides), the present disclosure provides oligonucleotides comprising a nucleobase, e.g., of a nucleoside opposite to a target nucleoside such as A, which is or comprises C, A, b007U, b001U, b001A, b002U, b001C, b003U, b002C, b004U, b003C, b005U, b002I, b006U, b003I, b008U, b009U, b002A, b003A, b001G, or zdnp. In some embodiments, a nucleobase is C. In some embodiments, a nucleobase is A. In some embodiments, a nucleobase is hypoxanthine. In some embodiments, a nucleobase is b002I. In some embodiments, a nucleobase is b003I. In some embodiments, a nucleobase is b004I. In some embodiments, a nucleobase is b014I. In some embodiments, a nucleobase is b001C. In some embodiments, a nucleobase is b002C. In some embodiments, a nucleobase is b003C. In some embodiments, a nucleobase is b004C. In some embodiments, a nucleobase is b005C. In some embodiments, a nucleobase is b006C. In some embodiments, a nucleobase is b007C. In some embodiments, a nucleobase is b008C. In some embodiments, a nucleobase is b009C. In some embodiments, a nucleobase is b001U. In some embodiments, a nucleobase is b002U. In some embodiments, a nucleobase is b003U. In some embodiments, a nucleobase is b004U. In some embodiments, a nucleobase is b005U. In some embodiments, a nucleobase is b006U. In some embodiments, a nucleobase is b007U. In some embodiments, a nucleobase is b008U. In some embodiments, a nucleobase is b009U. In some embodiments, a nucleobase is b011U. In some embodiments, a nucleobase is b012U. In some embodiments, a nucleobase is b013U. In some embodiments, a nucleobase is b001A. In some embodiments, a nucleobase is b002A. In some embodiments, a nucleobase is b003A. In some embodiments, a nucleobase is b001G. In some embodiments, a nucleobase is b002G. In some embodiments, a nucleobase is or zdnp. In some embodiments, as those skilled in the art appreciate, a nucleobase is protected, e.g., for oligonucleotide synthesis. For example, in some embodiments, a nucleobase is protected b001A having the structure of



, wherein R' is as described herein. In some embodiments, R' is −C(O)R. In some embodiments, R' is −C(O)Ph.

[00279] In some embodiments, it was observed that various modified nucleobases, e.g., b001A, b008U, etc., can provide improved adenosine editing efficiency when compared to a reference nucleobase (e.g., under comparable conditions including, e.g., in otherwise identical oligonucleotides, assessed in identical or comparable assays, etc.). In some embodiments, a reference nucleobase is U. In some embodiments, a

reference nucleobase is T. In some embodiments, a reference nucleobase is C.

Certain modified nucleobases

[00280] In some embodiments, BA is or comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms. In some embodiments, Ring BA is or comprises an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, Ring BA is saturated. In some embodiments, Ring BA comprises one or more unsaturation. In some embodiments, Ring BA is partially unsaturated. In some embodiments, Ring BA is aromatic.

[00281] In some embodiments, BA is or comprises Ring BA, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms. In some embodiments, Ring BA is or comprises an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, Ring BA is saturated. In some embodiments, Ring BA comprises one or more unsaturation. In some embodiments, Ring BA is partially unsaturated. In some embodiments, Ring BA is aromatic.

[00282] In some embodiments, BA is or comprises Ring BA. In some embodiments, BA is Ring BA. In some embodiments, BA is or comprises a tautomer of Ring BA. In some embodiments, BA is a tautomer of Ring BA.

[00283] In some embodiments, structures of the present disclosure contain one or more optionally substituted rings (e.g., Ring BA, −Cy−, Ring BA^A, R, formed by R groups taken together, etc.). In some embodiments, a ring is an optionally substituted C_{3-30}, C_{3-20}, C_{3-15}, C_{3-10}, C_{3-9}, C_{3-8}, C_{3-7}, C_{3-6}, C_{5-50}, C_{5-20}, C_{5-15}, C_{5-10}, C_{5-9}, C_{5-8}, C_{5-7}, C_{5-6}, or 3-30 (e.g., 3-30, 3-20, 3-15, 3-10, 3-9, 3-8, 3-7, 3-6, 5-50, 5-20, 5-15, 5-10, 5-9, 5-8, 5-7, 5-6, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, etc.) membered monocyclic, bicyclic or polycyclic ring having 0-10 (e.g., 1-10, 1-5, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) heteroatoms. In some embodiments, a ring is an optionally substituted 3-10 membered monocyclic or bicyclic, saturated, partially saturated or aromatic ring having 0-3 heteroatoms. In some embodiments, a ring is substituted. In some embodiments, a ring is not substituted. In some embodiments, a ring is 3, 4, 5, 6, 7, 8, 9, or 10 membered. In some embodiments, a ring is 5, 6, or7-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is monocyclic. In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, a ring is saturated. In some embodiments, a ring contains at least one unsaturation. In some embodiments, a ring is partially unsaturated. In some embodiments, a ring is aromatic. In some embodiments, a ring has 0-5 heteroatoms. In some embodiments, a ring has 1-5 heteroatoms. In some embodiments, a ring has one or more heteroatoms. In some embodiments, a ring has 1 heteroatom. In some embodiments, a ring has 2 heteroatoms. In some embodiments, a ring has 3 heteroatoms. In some embodiments, a ring has 4 heteroatoms. In some embodiments, a ring has 5 heteroatoms. In some

embodiments, a heteroatom is nitrogen. In some embodiments, a heteroatom is oxygen. In some embodiments, a ring is substituted, e.g., substituted with one or more alkyl groups and optionally one or more other substituents as described herein. In some embodiments, a substituent is methyl.

[00284] In some embodiments, each monocyclic ring unit of a monocyclic, bicyclic, or polycyclic ring of the present disclosure (e.g., Ring BA, −Cy−, Ring BA^A, R, formed by R groups taken together, etc.) is independently an optionally substituted 5-7 membered, saturated, partially unsaturated or aromatic ring having 0-5 heteroatoms. In some embodiments, one or more monocyclic units independently comprise one or more unsaturation. In some embodiments, one or more monocyclic units are saturated. In some embodiments, one or more monocyclic units are partially saturated. In some embodiments, one or more monocyclic units are aromatic. In some embodiments, one or more monocyclic units independently have 1-5 heteroatoms. In some embodiments, one or more monocyclic units independently have at least one nitrogen atom. In some embodiments, each monocyclic unit is independently 5- or 6-membered. In some embodiments, a monocyclic unit is 5-membered. In some embodiments, a monocyclic unit is 5-membered and has 1-2 nitrogen atom. In some embodiments, a monocyclic unit is 6-membered. In some embodiments, a monocyclic unit is 6-membered and has 1-2 nitrogen atom. Rings and monocyclic units thereof are optionally substituted unless otherwise specified.

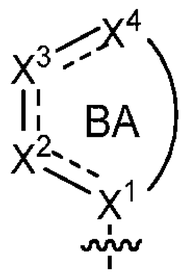
[00285] Without the intention to be limited by any particular theory, the present disclosure recognizes that in some embodiment, structures of nucleobases (e.g. BA) can impact interactions with proteins (e.g., ADAR proteins such as ADAR1, ADAR2, etc.). In some embodiments, provided oligonucleotides comprise nucleobases that can facility interaction of an oligonucleotide with an enzyme, e.g., ADAR1. In some embodiments, provided oligonucleotides comprise nucleobases that may reduce strength of base pairing (e.g., compared to A−T/U or C−G). In some embodiments, the present disclosure recognizes that by maintaining and/or enhancing interactions (e.g., hydrogen bonding) of a first nucleobase with a protein (e.g., an enzyme like ADAR1) and/or reducing interactions (e.g., hydrogen bonding) of a first nucleobase with its corresponding nucleobase (e.g., A) on the other strand in a duplex, modification of the corresponding nucleobase by a protein (e.g., an enzyme like ADAR1) can be significantly improved. In some embodiments, the present disclosure provides oligonucleotides comprises such a first nucleobase (e.g., various embodiments of BA described herein). Exemplary embodiments of such as a first nucleobase are as described herein. In some embodiments, when an oligonucleotide comprising such a first nucleobase is aligned with another nucleic acid for maximum complementarity, the first nucleobase is opposite to A. In some embodiments, such an A opposite to the first nucleobase, as exemplified in many embodiments of the present disclosure, can be efficiently modified using technologies of the present disclosure.

[00286] In some embodiments, Ring BA comprises a moiety $=\!\!=\!\!-X^2=\!\!-\!\!=X^3=\!\!=$, wherein each variable is independently as described herein. In some embodiments, Ring BA comprises a moiety $=\!\!=\!\!X^2=\!\!=\!\!X^3=\!\!=\!\!X^4=\!\!=$, wherein each variable is independently as described herein. In some embodiments, Ring BA comprises a moiety $-X^1(=\!\!=)=\!\!=X^2=\!\!=\!\!X^3=\!\!=$, wherein each variable is independently as described herein. In some

embodiments, Ring BA comprises a moiety $-X^1(=)=X^2=X^3=X^4=$, wherein each variable is independently as described herein. In some embodiments, X^1 is bonded to a sugar. In some embodiments, X^1 is $-N(-)-$. In some embodiments, X^1 is $-C(=)-$. In some embodiments, X^2 is $-C(O)-$. In some embodiments, X^3 is $-NH-$. In some embodiments, X^4 is not $-C(O)-$. In some embodiments, X^4 is $-C(O)-$, and forms an intramolecular hydrogen bond, e.g., with a moiety of the same nucleotidic unit (e.g., within the same BA unit (e.g., with a hydrogen bond donor (e.g., $-OH$, SH, etc.) of X^5). In some embodiments, X^4 is $-C(=NH)-$. In some embodiments, Ring BA comprises a moiety $=X^{4'}=X^{5'}=$, wherein each variable is independently as described herein. In some embodiments, $X^{4'}$ is $-C(O)-$. In some embodiments, $X^{5'}$ is $-NH-$.

[00287] In some embodiments, BA is optionally substituted or protected C or a tautomer thereof. In some embodiments, BA is optionally substituted or optionally protected C. In some embodiments, BA is an optionally substituted or optionally protected tautomer of C. In some embodiments, BA is C. In some embodiments, BA is substituted C. In some embodiments, BA is protected C. In some embodiments, BA is an substituted tautomer of C. In some embodiments, BA is an protected tautomer of C.

[00288] In some embodiments, Ring BA has the structure of formula BA-I:



,

BA-I

wherein:

Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic, saturated, partially saturated or aromatic ring having 1-10 heteroatoms;

each $=$ is independent a single or double bond;

X^1 is $-N(-)-$ or $-C(-)=$;

X^2 is $-C(O)-$, $-C(R^{B2})=$, or $-C(OR^{B2})=$, wherein R^{B2} is $-L^{B2}-R'$;

X^3 is $-N(R^{B3})-$ or $-N=$, wherein R^{B3} is $-L^{B3}-R'$;

X^4 is $-C(R^{B4})=$, $-C(-N(R^{B4})_2)=$, $-C(R^{B4})_2-$, $-C(O)-$, or $-C(=NR^{B4})-$, wherein each R^{B4} is independently $-L^{B4}-R^{B41}$, or two R^{B4} on the same atom are taken together to form $=O$, $=C(-L^{B4}-R^{B41})_2$, $=N-L^{B4}-R^{B41}$, or optionally substituted $=CH_2$ or $=NH$, wherein each R^{B41} is independently R';

each of L^{B2}, L^{B3}, and L^{B4} is independently L^B;

each L^B is independently a covalent bond, or an optionally substituted bivalent C_{1-10} saturated or partially unsaturated chain having 0-6 heteroatoms, wherein one or more methylene unit is optionally and independently replaced with $-Cy-$, $-O-$, $-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, or $-C(O)O-$;

each $-Cy-$ is independently an optionally substituted, 3-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R' is independently −R, −C(O)R, −C(O)OR, −C(O)N(R)$_2$, or −SO$_2$R; and

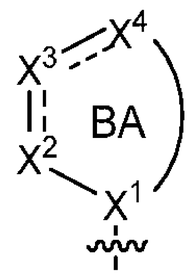
each R is independently −H, or an optionally substituted group selected from C$_{1-20}$ aliphatic, C$_{1-20}$ heteroaliphatic having 1-10 heteroatoms, C$_{6-20}$ aryl, C$_{6-20}$ arylaliphatic, C$_{6-20}$ arylheteroaliphatic having 1-10 heteroatoms, 5-20 membered heteroaryl having 1-10 heteroatoms, and 3-20 membered heterocyclyl having 1-10 heteroatoms, or:

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or:

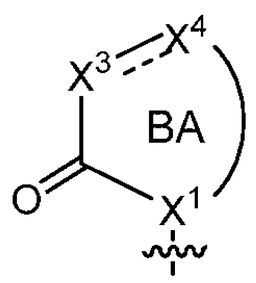
two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00289] In some embodiments, Ring BA (e.g., one of formula BA-I) has the structure of formula BA-I-a:



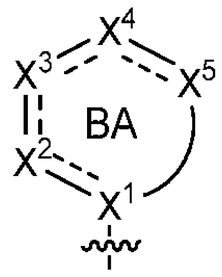
BA-I-a

[00290] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, etc.)has the structure of formula BA-I-b:



BA-I-b

[00291] In some embodiments, Ring BA (e.g., one of formula BA-I) has the structure of formula BA-II:



BA-II

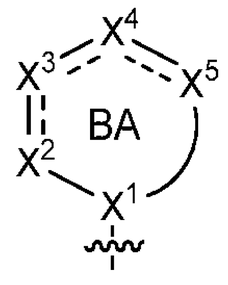
wherein:

X^5 is $-C(R^{B5})_2-$, $-N(R^{B5})-$, $-C(R^{B5})=$, $-C(O)-$, or $-N=$, wherein each R^{B5} is independently halogen, or $-L^{B5}-R^{B51}$, wherein R^{B51} is $-R'$, $-N(R')_2$, $-OR'$, or $-SR'$;

L^{B5} is L^B; and

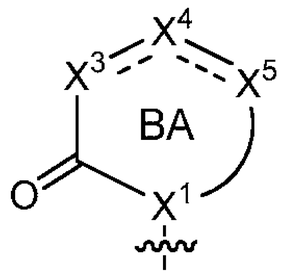
each other variable is independently as described herein.

[00292] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-II, etc.) has the structure of formula BA-II-a:



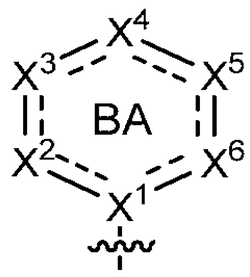
BA-II-a

[00293] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, etc.) has the structure of formula BA-II-b:



BA-II-b

[00294] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-II, etc.) has the structure of formula BA-III:



BA-III

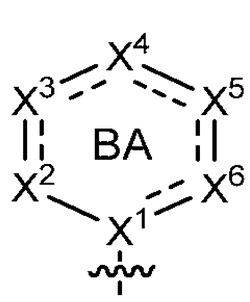
wherein:

X^6 is $-C(R^{B6})=$, $-C(OR^{B6})=$, $-C(R^{B6})_2-$, $-C(O)-$ or $-N=$, wherein each R^{B6} is independently $-L^{B6}-R^{B61}$, or two R^{B6} on the same atom are taken together to form $=O$, $=C(-L^{B6}-R^{B61})_2$, $=N-L^{B6}-R^{B61}$, or optionally substituted $=CH_2$ or $=NH$, wherein each R^{B61} is independently R';

L^{B6} is L^B; and

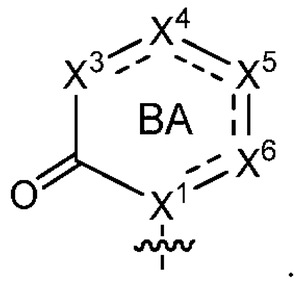
each other variable is independently as described herein.

[00295] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-II, BA-II-a, BA-III, etc.) has the structure of formula BA-III-a:



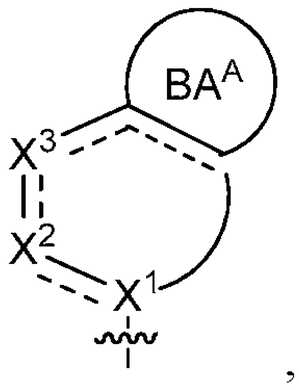
BA-III-a

[00296] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, etc.) has the structure of formula BA-III-b:



BA-III-b

[00297] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-II, etc.) has the structure of formula BA-IV:



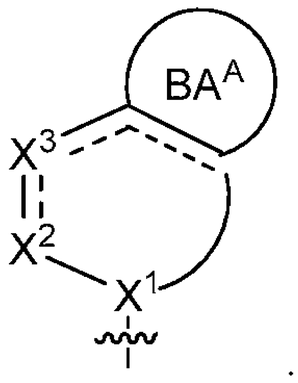
BA-IV

wherein:

Ring BA^A is an optionally substituted 5-14 membered, monocyclic, bicyclic or polycyclic ring having 0-5 heteroatoms, and

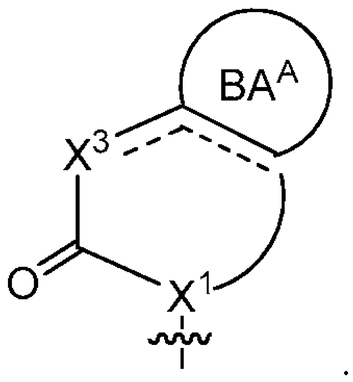
each other variable is independently as described herein.

[00298] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-II, BA-II-a, etc.) has the structure of formula BA-IV-a:



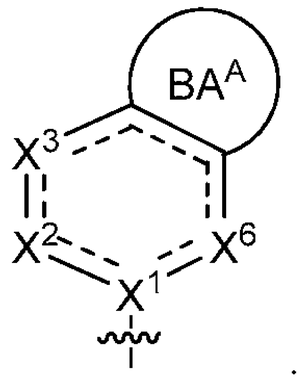
BA-IV-a

[00299] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-II, BA-II-a, etc.) has the structure of formula BA-IV-b:



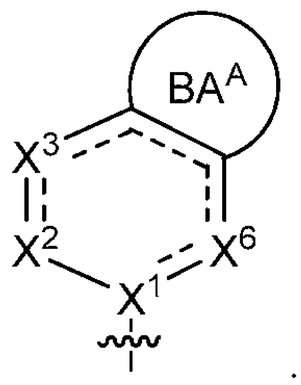
BA-IV-b

[00300] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-II, BA-III, BA-IV, etc.) has the structure of formula BA-V:



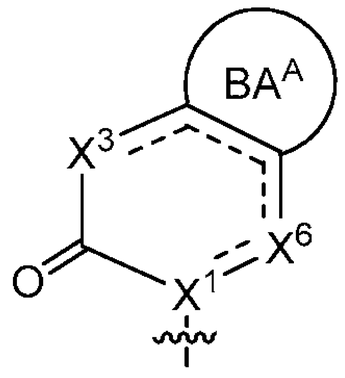
BA-V

[00301] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-II, BA-II-a, BA-III, BA-III-a, BA-IV, BA-IV-a, BA-V, etc.) has the structure of formula BA-V-a:



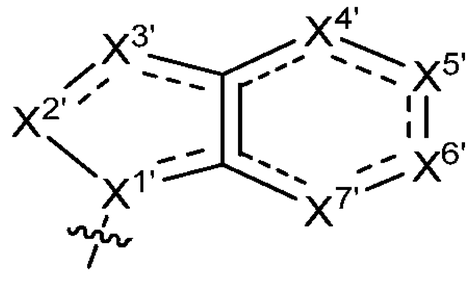
BA-V-a

[00302] In some embodiments, Ring BA (e.g., one of formula BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, etc.) has the structure of formula BA-V-a:



BA-V-b

[00303] In some embodiments, Ring BA has the structure of formula BA-VI:



BA-VI

wherein:

$X^{1'}$ is $-N(-)-$ or $-C(-)=$;

$X^{2'}$ is $-C(O)-$ or $-C(R^{B2'})=$, wherein $R^{B2'}$ is $-L^{B2'}-R'$;

each ═ is independent a single or double bond;

$X^{3'}$ is $-N(R^{B3'})-$ or $-N=$, wherein $R^{B3'}$ is $-L^{B3'}-R'$;

$X^{4'}$ is $-C(R^{B4'})=$, $-C(OR^{B4'})=$, $-C(-N(R^{B4'})_2)=$, $-C(R^{B4'})_2-$, $-C(O)-$, or $-C(=NR^{B4'})-$, wherein each $R^{B4'}$ is independently $-L^{B4'}-R^{B41'}$, or two $R^{B4'}$ on the same atom are taken together to form =O,

$=C(-L^{B4'}-R^{B41'})_2$, $=N-L^{B4'}-R^{B41'}$, or optionally substituted $=CH_2$ or =NH, wherein each $R^{B41'}$ is independently −R';

$X^{5'}$ is $-N(R^{B5'})-$ or −N=, wherein $R^{B5'}$ is $-L^{B5'}-R'$;

$X^{6'}$ is $-C(R^{B6'})=$, $-C(OR^{B6'})=$, $-C(R^{B6'})_2-$, −C(O)− or −N=, wherein each $R^{B6'}$ is independently $-L^{B6'}-R^{B61'}$, or two $R^{B6'}$ on the same atom are taken together to form =O, $=C(-L^{B6'}-R^{B61'})_2$, $=N-L^{B6'}-R^{B61'}$, or optionally substituted $=CH_2$ or =NH, wherein each $R^{B61'}$ is independently R';

$X^{7'}$ is $-C(R^{B7'})=$, $-C(OR^{B6'})=$, $-C(R^{B7'})_2-$, −C(O)−, $-N(R^{B7'})-$, or −N=, wherein each $R^{B7'}$ is independently $-L^{7'}-R^{B71'}$, or two $R^{B7'}$ on the same atom are taken together to form =O, $=C(-L^{7'}-R^{B71'})_2$, $=N-L^{7'}-R^{B71'}$, or optionally substituted $=CH_2$ or =NH, wherein each $R^{B71'}$ is independently R';

each of $L^{B2'}$, $L^{B3'}$, $L^{B4'}$, $L^{B5'}$ and $L^{B6'}$ is independently L^B; and

each other variable is independently as described herein.

[00304] In some embodiments, ⎓ is a single bond. In some embodiments, ⎓ is a double bond.

[00305] In some embodiments, X^1 is −(N−)−. In some embodiments, X^1 is −C(−)=.

[00306] In some embodiments, X^2 is −C(O)−. In some embodiments, X^2 is $-C(R^{B2})=$. In some embodiments, X^2 is $-C(OR^{B2})=$. In some embodiments, X^2 is −CH=.

[00307] In some embodiments, L^{B2} is a covalent bond.

[00308] In some embodiments, R^{B2} is a protecting group, e.g., a hydroxyl protecting group suitable for oligonucleotide synthesis. In some embodiments, R^{B2} is R'. In some embodiments, R^{B2} is −H.

[00309] In some embodiments, X^3 is $-N(R^{B3})-$. In some embodiments, X^3 is −NH−. In some embodiments, X^3 is −N=.

[00310] In some embodiments, L^{B3} is a covalent bond.

[00311] In some embodiments, R^{B3} is a protecting group, e.g., an amino protecting group suitable for oligonucleotide synthesis (e.g., Bz). In some embodiments, R^{B3} is R'. In some embodiments, R^{B3} is −C(O)R. In some embodiments, R^{B3} is R. In some embodiments, R^{B3} is −H.

[00312] In some embodiments, X^4 is $-C(R^{B4})=$. In some embodiments, X^4 is −C(R)=. In some embodiments, X^4 is −CH=. In some embodiments, X^4 is $-C(OR^{B4})=$. In some embodiments, X^4 is $-C(-N(R^{B4})_2)=$. In some embodiments, X^4 is $-C(-NHR^{B4})=$. In some embodiments, X^4 is −C(−NHR')=. In some embodiments, X^4 is −C(−NHR')=. In some embodiments, X^4 is $-C(-NH_2)=$. In some embodiments, X^4 is $-C(-NHC(O)R)=$. In some embodiments, X^4 is $-C(R^{B4})_2-$. In some embodiments, X^4 is $-CH_2-$. In some embodiments, X^4 is −C(O)−. In some embodiments, X^4 is −C(O)−, wherein O forms a intramolecular hydrogen bond. In some embodiments, O forms a hydrogen bond with a hydrogen bond donor of X^5 of the same BA. In some embodiments, X^4 is $-C(=NR^{B4})-$. In some embodiments, X^4 is $-C((=NR^{B4})-$, wherein N forms a intramolecular hydrogen bond. In some embodiments, N forms a hydrogen bond with a hydrogen bond donor of X^5 of the same BA.

[00313] In some embodiments, R^{B4} $-L^{B4}-R^{B41}$. In some embodiments, two R^{B4} on the same atom are taken together to form =O, $=C(-L^{B4}-R^{B41})_2$, $=N-L^{B4}-R^{B41}$, or optionally substituted $=CH_2$ or =NH.

[00314] In some embodiments, two R^{B4} on the same atom are taken together to form =O. In some embodiments, two R^{B4} on the same atom are taken together to form $=C(-L^{B4}-R^{B41})_2$. In some embodiments, $=C(-L^{B4}-R^{B41})_2$ is $=CH-L^{B4}-R^{B41}$. In some embodiments, $=C(-L^{B4}-R^{B41})_2$ is =CHR'. In some embodiments, $=C(-L^{B4}-R^{B41})_2$ is =CHR. In some embodiments, two R^{B4} on the same atom are taken together to form $=N-L^{B4}-R^{B41}$. In some embodiments, $=N-L^{B4}-R^{B41}$ is =N−R. In some embodiments, two R^{B4} on the same atom are taken together to form $=CH_2$. In some embodiments, two R^{B4} on the same atom are taken together to form =NH. In some embodiments, a formed group is a suitable protecting group, e.g., amino protecting group, for oligonucleotide synthesis.

[00315] In some embodiments, X^4 is $-C(-N=C(-L^{B4}-R^{B41})_2)=$. In some embodiments, X^4 is $-C(-N=CH-L^{B4}-R^{B41})=$. In some embodiments, X^4 is $-C(-N=CH-N(CH_3)_2)=$.

[00316] In some embodiments, R of X^4 (e.g., of $-C(=N-R)-$, $=C(R)-$, etc.) are optionally taken together with another R, e.g., of X^5, to form a ring as described herein.

[00317] In some embodiments, R^{B4} is R'. In some embodiments, R^{B4} is R. In some embodiments, R^{B4} is −H.

In some embodiments, R^{B4} is a protecting group, e.g., an amino or hydroxyl protecting group suitable for oligonucleotide synthesis. In some embodiments, R^{B4} is R'. In some embodiments, R^{B4} is $-CH_2CH_2-$(4-nitrophenyl).

[00318] In some embodiments, L^{B4} is a covalent bond. In some embodiments, L^{B4} is not a covalent bond. In some embodiments, at least one methylene unit is replaced with $-C(O)-$. In some embodiments, at least one methylene unit is replaced with $-C(O)N(R')-$. In some embodiments, at least one methylene unit is replaced with $-N(R')-$. In some embodiments, at least one methylene unit is replaced with −NH−. In some embodiments, L^{B4} is or comprises optionally substituted −N=CH−.

[00319] In some embodiments, R^{B41} is R'. In some embodiments, R^{B41} is −H. In some embodiments, R^{B41} is R. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

[00320] In some embodiments, X^5 is $-C(R^{B5})_2-$. In some embodiments, X^5 is $-ChR^{B5}-$. In some embodiments, X^5 is $-CH_2-$. In some embodiments, X^5 is $-N(R^{B5})-$. In some embodiments, X^5 is −NH−. In some embodiments, X^5 is $-C(R^{B5})=$. In some embodiments, X^5 is $-C(R)=$. In some embodiments, X^5 is −CH=. In some embodiments, X^5 is −N=. In some embodiments, X^5 is –C(O)−.

[00321] In some embodiments, R^{B5} is halogen. In some embodiments, R^{B5} is $-L^{B5}-R^{B51}$. In some embodiments, R^{B5} is $-L^{B5}-R^{B51}$, wherein R^{B51} is R', −NHR', −OH, or −SH. In some embodiments, R^{B5} is $-L^{B5}-R^{B51}$, wherein R^{B51} is −NHR, −OH, or −SH. In some embodiments, R^{B5} is $-L^{B5}-R^{B51}$, wherein R^{B51} is $-NH_2$, −OH, or −SH. In some embodiments, R^{B5} is $-C(O)-R^{B51}$. In some embodiments, R^{B5} is R'. In some embodiments, R^{B5} is R. In some embodiments, R^{B5} is −H. In some embodiments, R^{B5} is −OH. In some embodiments, R^{B5} is $-CH_2OH$.

[00322] In some embodiments, when X^4 is $-C(O)-$, X^5 is $-C(R^{B5})_2-$, $-C(R^{B5})=$, or $-N(R^{B5})-$, wherein R^{B5} is $-L^{B5}-R^{B51}$, wherein R^{B51} is −NHR', −OH, or −SH. In some embodiments, X^4 is $-C(O)-$, and R^{B51} is or

comprises a hydrogen bond donor, which forms a hydrogen bond with the O of X^4.

[00323] In some embodiments, L^{B5} is a covalent bond. In some embodiments, L^{B5} is or comprises −C(O)−. In some embodiments, L^{B5} is or comprises −O−. In some embodiments, L^{B5} is or comprises −OC(O)−. In some embodiments, L^{B5} is or comprises $-CH_2OC(O)-$.

[00324] In some embodiments, R^{51} is −R'. In some embodiments, R^{51} is −R. In some embodiments, R^{51} is −H. In some embodiments, R^{51} is $-N(R')_2$. In some embodiments, R^{51} is −NHR'. In some embodiments, R^{51} is −NHR. In some embodiments, R^{51} is $-NH_2$. In some embodiments, R^{51} is −OR'. In some embodiments, R^{51} is −OR. In some embodiments, R^{51} is −OH. In some embodiments, R^{51} is −SR'. In some embodiments, R^{51} is −SR. In some embodiments, R^{51} is −SH. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is methyl.

[00325] In some embodiments, R^{B5} is $-C(O)-R^{B51}$. In some embodiments, R^{B5} is $-C(O)NHCH_2Ph$. In some embodiments, R^{B5} is −C(O)NHPh. In some embodiments, R^{B5} is $-C(O)NHCH_3$. In some embodiments, R^{B5} is $-OC(O)-R^{B51}$. In some embodiments, R^{B5} is −OC(O)−R. In some embodiments, R^{B5} is $-OC(O)CH_3$.

[00326] In some embodiments, X^5 is directly bonded to X^1, and Ring BA is 5-membered.

[00327] In some embodiments, X^6 is $-C(R^{B6})=$. In some embodiments, X^6 is −CH=. In some embodiments, X^6 is $-C(OR^{B6})=$. In some embodiments, X^6 is $-C(R^{B6})_2-$. In some embodiments, X^6 is $-CH_2-$. In some embodiments, X^6 is −C(O)−. In some embodiments, X^6 is −N=.

[00328] In some embodiments, R^{B6} is $-L^{B6}-R^{B61}$. In some embodiments, two R^{B6} on the same atom are taken together to form =O, $=C(-L^{B6}-R^{B61})_2$, $=N-L^{B6}-R^{B61}$, or optionally substituted $=CH_2$ or =NH. In some embodiments, two R^{B6} on the same atom are taken together to form =O. In some embodiments, L^{B6} is a covalent bond. In some embodiments, R^{B6} is R. In some embodiments, R^{B6} is −H.

[00329] In some embodiments, R^{B6} is a protecting group, e.g., an amino or hydroxyl protecting group suitable for oligonucleotide synthesis. In some embodiments, R^{B6} is R. In some embodiments,

[00330] In some embodiments, L^{B6} is a covalent bond. In some embodiments, L^{B6} is optionally substituted C_{1-10} alkylene. In some embodiments, L^{B6} is $-CH_2CH_2-$. In some embodiments, R^{B6} is $-CH_2CH_2-$(4-nitrophenyl).

[00331] In some embodiments, R^{B61} is R'. In some embodiments, R^{B61} is R. In some embodiments, R^{B61} is −H.

[00332] In some embodiments, Ring BA^A is 5-membered. In some embodiments, Ring BA^A is 5-membered. In some embodiments, Ring BA^A has one heteroatom. In some embodiments, Ring BA^A has 2 heteroatoms. In some embodiments, a heteroatom is nitrogen. In some embodiments, a heteroatom is oxygen.

[00333] In some embodiments, $X^{1'}$ is −(N−)−. In some embodiments, $X^{1'}$ is −C(−)=.

[00334] In some embodiments, $X^{2'}$ is −C(O)−. In some embodiments, $X^{2'}$ is $-C(R^{B2'})=$. In some embodiments, $X^{2'}$ is −CH=.

[00335] In some embodiments, $L^{B2'}$ is a covalent bond.

[00336] In some embodiments, $R^{B2'}$ is R'. In some embodiments, $R^{B2'}$ is R. In some embodiments, $R^{B2'}$

is −H. In some embodiments, $X^{2'}$ is −CH=.

[00337] In some embodiments, $X^{3'}$ is $-N(R^{B3'})-$. In some embodiments, $X^{3'}$ is $-N(R')-$. In some embodiments, $X^{3'}$ is −NH−. In some embodiments, $X^{3'}$ is −N=.

[00338] In some embodiments, $L^{B3'}$ is a covalent bond.

[00339] In some embodiments, $R^{B3'}$ is R'. In some embodiments, $R^{B3'}$ is R. In some embodiments, $R^{B3'}$ is −H.

[00340] In some embodiments, $X^{4'}$ is $-C(R^{B4'})=$. In some embodiments, $X^{4'}$ is $-C(OR^{B4'})=$. In some embodiments, $X^{4'}$ is $-C(-N(R^{B4'})_2)=$. In some embodiments, $X^{4'}$ is $-C(-NHR^{B4'})=$. In some embodiments, $X^{4'}$ is $-C(-NH_2)=$. In some embodiments, $X^{4'}$ is $-C(-NHR')=$. In some embodiments, $X^{4'}$ is −C(−NHC(O)R)=. In some embodiments, $X^{4'}$ is $-C(R^{B4'})_2-$. In some embodiments, $X^{4'}$ is −C(O)−. In some embodiments, $X^{4'}$ is $-C(=NR^{B4'})-$.

[00341] In some embodiments, $R^{B4'}$ is $-L^{B4'}-R^{B41'}$. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form =O, $=C(-L^{B4'}-R^{B41'})_2$, $=N-L^{B4'}-R^{B41'}$, or optionally substituted $=CH_2$ or =NH. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form =O. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form $=C(-L^{B4'}-R^{B41'})_2$. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form $=N-L^{B4'}-R^{B41'}$. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form $=CH_2$. In some embodiments, two $R^{B4'}$ on the same atom are taken together to form =NH. In some embodiments, a formed group is a suitable protecting group, e.g., amino protecting group, for oligonucleotide synthesis.

[00342] In some embodiments, $X^{4'}$ is $-C(-N=C(-L^{B4'}-R^{B41'})_2)=$. In some embodiments, $X^{4'}$ is $-C(-N=CH-L^{B4'}-R^{B41'})=$. In some embodiments, $X^{4'}$ is $-C(-N=CH-N(CH_3)_2)=$.

[00343] In some embodiments, $R^{B4'}$ is R'. In some embodiments, $R^{B4'}$ is R. In some embodiments, $R^{B4'}$ is −H.

[00344] In some embodiments, $R^{B4'}$ is a protecting group, e.g., an amino or hydroxyl protecting group suitable for oligonucleotide synthesis. In some embodiments, $R^{B4'}$ is R'. In some embodiments, $R^{B4'}$ is $-CH_2CH_2-$(4-nitrophenyl).

[00345] In some embodiments, $L^{B4'}$ is a covalent bond. In some embodiments, $L^{B4'}$ is optionally substituted C_{1-10} alkylene. In some embodiments, $L^{B4'}$ is $-CH_2CH_2-$. In some embodiments, at least one methylene unit is replaced with $-N(R')-$. In some embodiments, R' is R. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is methyl. In some embodiments, R is −H.

[00346] In some embodiments, $R^{B41'}$ is R'. In some embodiments, $R^{B41'}$ is R. In some embodiments, $R^{B41'}$ is −H.

[00347] In some embodiments, $X^{5'}$ is $-N(R^{B5'})-$. In some embodiments, $X^{5'}$ is −NH−. In some embodiments, $X^{5'}$ is −N=.

[00348] In some embodiments, $L^{B5'}$ is a covalent bond.

[00349] In some embodiments, $R^{B5'}$ is R'. In some embodiments, $R^{B5'}$ is R. In some embodiments, $R^{B5'}$ is −H.

[00350] In some embodiments, $X^{6'}$ is $-C(R^{B6'})=$. In some embodiments, $X^{6'}$ is −CH=. In some embodiments, $X^{6'}$ is $-C(OR^{B6'})=$. In some embodiments, $X^{6'}$ is $-C(R^{B6'})_2-$. In some embodiments, $X^{6'}$ is −C(O)−. In some embodiments, $X^{6'}$ is −N=.

[00351] In some embodiments, $R^{B6'}$ is $-L^{B6'}-R^{B61'}$. In some embodiments, two $R^{B6'}$ on the same atom are taken together to form =O, $=C(-L^{B6'}-R^{B61'})_2$, $=N-L^{B6'}-R^{B61'}$, or optionally substituted $=CH_2$ or =NH. In some embodiments, two $R^{B6'}$ on the same atom are taken together to form =O.

[00352] In some embodiments, $L^{B6'}$ is a covalent bond. In some embodiments, $L^{B6'}$ is optionally substituted C_{1-10} alkylene. In some embodiments, $L^{B6'}$ is $-CH_2CH_2-$.

[00353] In some embodiments, $R^{B6'}$ is R'. In some embodiments, $R^{B6'}$ is R. In some embodiments, $R^{B6'}$ is −H. In some embodiments, $R^{B6'}$ is a protecting group, e.g., an amino or hydroxyl protecting group suitable for oligonucleotide synthesis. In some embodiments, $R^{B6'}$ is R'. In some embodiments, $R^{B6'}$ is $-CH_2CH_2-$(4-nitrophenyl).

[00354] In some embodiments, $R^{B61'}$ is R'. In some embodiments, $R^{B61'}$ is R. In some embodiments, $R^{B61'}$ is −H.

[00355] In some embodiments, $X^{7'}$ is $-C(R^{B7'})=$. In some embodiments, $X^{7'}$ is −CH=. In some embodiments, $X^{7'}$ is $-C(OR^{B7'})=$. In some embodiments, $X^{7'}$ is $-C(R^{B7'})_2-$. In some embodiments, $X^{7'}$ is −C(O)−. In some embodiments, $X^{7'}$ is $-N(R^{B7'})-$. In some embodiments, $X^{7'}$ is −NH−. In some embodiments, $X^{7'}$ is −N=.

[00356] In some embodiments, $R^{B7'}$ is $-L^{7'}-R^{B71'}$. In some embodiments, two $R^{B7'}$ on the same atom are taken together to form =O, $=C(-L^{7'}-R^{B71'})_2$, $=N-L^{7'}-R^{B71'}$, or optionally substituted $=CH_2$ or =NH. In some embodiments, two $R^{B7'}$ on the same atom are taken together to form =O. In some embodiments, $L^{7'}$ is a covalent bond. In some embodiments, $R^{B7'}$ is R. In some embodiments, $R^{B7'}$ is −H.

[00357] In some embodiments, $R^{B71'}$ is R'. In some embodiments, $R^{B71'}$ is R. In some embodiments, $R^{B71'}$ is −H.

[00358] In some embodiments, L^B is a covalent bond. In some embodiments, L^B is an optionally substituted bivalent C_{1-10} saturated or partially unsaturated aliphatic chain, wherein one or more methylene unit is optionally and independently replaced with −Cy−, −O−, −S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, or −C(O)O−. In some embodiments, L^B is an optionally substituted bivalent C_{1-10} saturated or partially unsaturated heteroaliphatic chain having 1-6 heteroatoms, wherein one or more methylene unit is optionally and independently replaced with −Cy−, −O−, −S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, or −C(O)O−. In some embodiments, at least methylene unit is replaced. In some embodiments, L^B is optionally substituted C_{1-10} alkylene. In some embodiments, L^B is $-CH_2CH_2-$. In some embodiments, at least one methylene unit is

replaced with −C(O)−. In some embodiments, at least one methylene unit is replaced with −C(O)N(R')−. In some embodiments, at least one methylene unit is replaced with −N(R')−. In some embodiments, at least one methylene unit is replaced with −NH−. In some embodiments, at least one methylene unit is replaced with −Cy−. In some embodiments, L^B is or comprises optionally substituted −N=CH−. In some embodiments, L^B is or comprises −C(O)−. In some embodiments, L^B is or comprises −O−. In some embodiments, L^B is or comprises −OC(O)−. In some embodiments, L^B is or comprises $-CH_2OC(O)-$.

[00359] In some embodiments, each −Cy− is independently an optionally substituted, 3-20 membered, monocyclic, bicyclic or polycyclic, saturated, partially saturated or aromatic ring having 0-10 heteroatoms. Suitable monocyclic unit(s) of −Cy− are described herein. In some embodiments, −Cy− is monocyclic. In some embodiments, −Cy− is bicyclic. In some embodiments, −Cy− is polycyclic. In some embodiments, −Cy− is an optionally substituted bivalent 3-10 membered monocyclic, saturated or partially unsaturated ring having 0-5 heteroatoms. In some embodiments, −Cy− is an optionally substituted bivalent 5-10 membered aromatic ring having 0-5 heteroatoms. In some embodiments, −Cy− is optionally substituted phenylene. In some embodiments, −Cy− is phenylene.

[00360] In some embodiments, R' is R. In some embodiments, R' is −C(O)R. In some embodiments, R' is −C(O)OR. In some embodiments, R' is $-C(O)N(R)_2$. In some embodiments, R' is $-SO_2R$.

[00361] In some embodiments, R' in various structures is a protecting group (e.g., for amino, hydroxyl, etc.), e.g., one suitable for oligonucleotide synthesis. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is 4-nitrophenyl. In some embodiments, R is $-CH_2CH_2-$(4-nitrophenyl). In some embodiments, R' is $-C(O)NPh_2$.

[00362] In some embodiments, each R is independently −H, or an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-20 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, two R groups are optionally and independently taken together to form a covalent bond. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms. In some embodiments, two groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-20 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms. In some embodiments, two groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms. In some embodiments, a formed ring is monocyclic. In some embodiments, a formed ring is bicyclic. In some embodiments, a formed

ring is polycyclic. In some embodiments, each monocyclic ring unit is independently 3-10 (e.g., 3-8, 3-7, 3-6, 5-10, 5-8, 5-7, 5-6, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) membered, and is independently saturated, partially saturated, or aromatic, and independently has 0-5 heteroatom. In some embodiments, a ring is saturated. In some embodiments, a ring is partially saturated. In some embodiments, a ring is aromatic. In some embodiments, a formed ring has 1-5 heteroatom. In some embodiments, a formed ring has 1 heteroatom. In some embodiments, a formed ring has 2 heteroatoms. In some embodiments, a heteroatom is nitrogen. In some embodiments, a heteroatom is oxygen.

[00363] In some embodiments, R is −H.

[00364] In some embodiments, R is optionally substituted C_{1-20}, C_{1-15}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, or C_{1-2} aliphatic. In some embodiments, R is optionally substituted alkyl. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is optionally substituted cycloaliphatic. In some embodiments, R is optionally substituted cycloalkyl.

[00365] In some embodiments, R is optionally substituted C_{1-20} heteroaliphatic having 1-10 heteroatoms.

[00366] In some embodiments, R is optionally substituted C_{6-20} aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

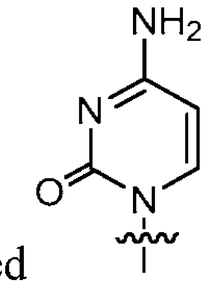
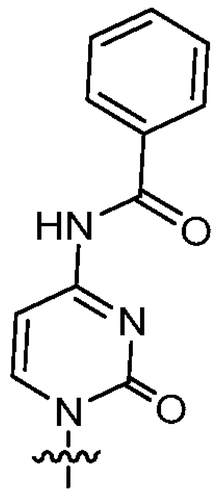
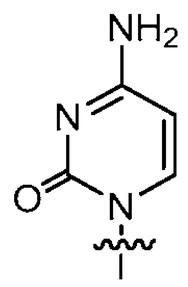
[00367] In some embodiments, R is optionally substituted C_{6-20} arylaliphatic. In some embodiments, R is optionally substituted C_{6-20} arylalkyl. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted C_{6-20} arylheteroaliphatic having 1-10 heteroatoms.

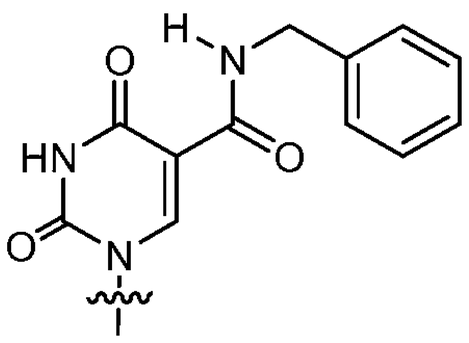
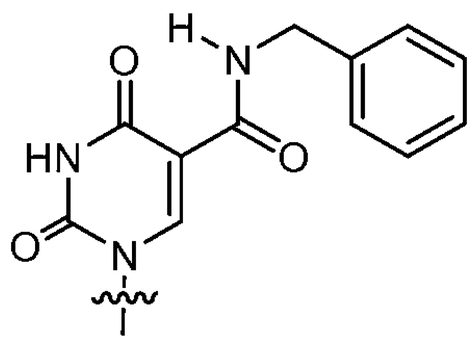
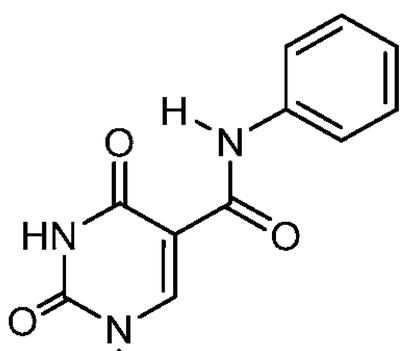
[00368] In some embodiments, R is optionally substituted 5-20 membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 3-20 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 3-10 membered heterocyclyl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 5-6 membered heterocyclyl having 1-5 heteroatoms. In some embodiments, a heterocyclyl is saturated. In some embodiments, a heterocyclyl is partially saturated.

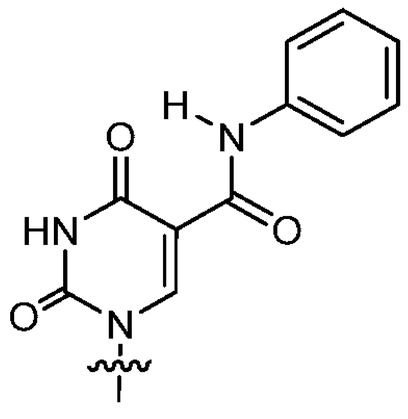
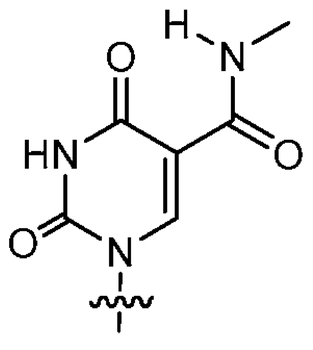
[00369] In some embodiments, a heteroatom is selected from boron, nitrogen, oxygen, sulfur, silicon and phosphorus. In some embodiments, a heteroatom is selected from nitrogen, oxygen, sulfur, and silicon. In some embodiments, a heteroatom is selected from nitrogen, oxygen, and sulfur. In some embodiments, a heteroatom is nitrogen. In some embodiments, a heteroatom is oxygen. In some embodiments, a heteroatom is sulfur.

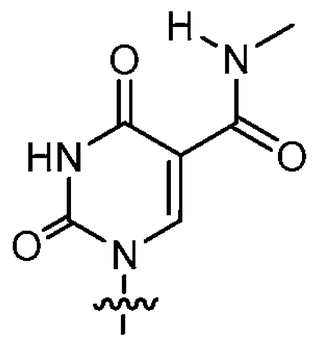
[00370] As appreciated by those skilled in the art, embodiments described for variables can be readily combined to provide various structures. Those skilled in the art also appreciates that embodiments described for a variable can be readily utilized for other variables that can be that variable, e.g., embodiments of R for R' R^{B2}, R^{B3}, R^{B4}, R^{B5}, R^{B6}, $R^{B2'}$, $R^{B3'}$, $R^{B4'}$, $R^{B5'}$, $R^{B6'}$, etc.; embodiments of embodiments of L^B for L^{B2}, L^{B3}, L^{B4}, L^{B5}, L^{B6}, $L^{B2'}$, $L^{B3'}$, $L^{B4'}$, $L^{B5'}$, $L^{B6'}$, etc. Exemplary embodiments and combinations thereof include but

are not limited to structures exemplified herein. Certain examples are described below.

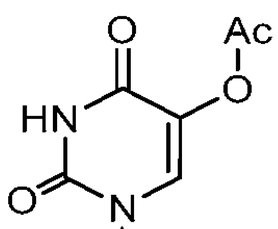
[00371] For example, in some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  .

[00372] In some embodiments, X^4 is −C(O)−, and O in −C(O)− of X^4 may form a hydrogen bond with a −H of R^5, e.g., a −H in −NHR', −OH, or −SH of $R^{5'}$. In some embodiments, X^4 is −C(O)−, and X^5 is −C(R^5)=. In some embodiments, $R^{5'}$ is −NHR'. In some embodiments, R^5 is −L^{B5}−NHR'. In some embodiments, L^{B5} is optionally substituted −CH_2−. In some embodiments, a methylene unit is replaced with −C(O)−. In some embodiments, L^{B5} is −C(O)−. In some embodiments, R' is optionally substituted methyl. In some embodiments, R' is −CH_2Ph. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is phenyl. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is optionally substituted methyl. In some embodiments, R' is methyl. In some embodiments, Ring BA is optionally protected  . In some embodiments, Ring BA is  . In some embodiments, 

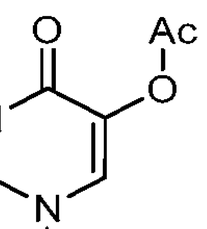
Ring BA is optionally protected . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally protected  . In some



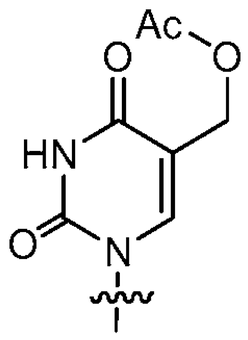
embodiments, Ring BA is . In some embodiments, Ring BA is optionally protected



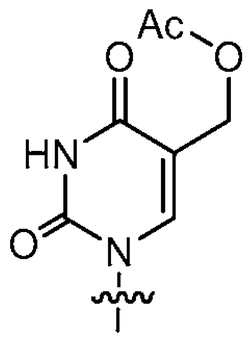
. In some embodiments, Ring BA is



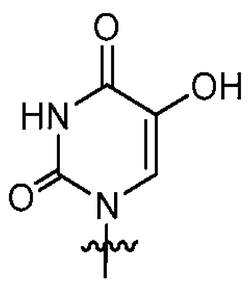
. In some embodiments, Ring BA is optionally protected



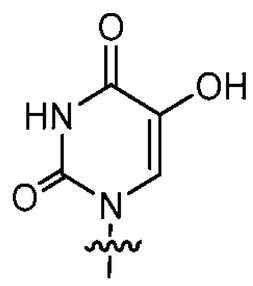
. In some embodiments, Ring BA is



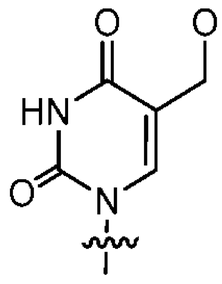
. In some embodiments, Ring BA is optionally protected



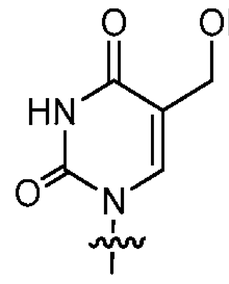
. In some embodiments, Ring BA is



. In some embodiments, Ring BA is optionally protected



. In some embodiments, Ring BA is

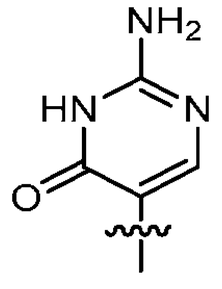


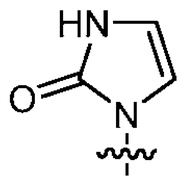
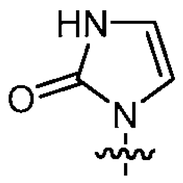
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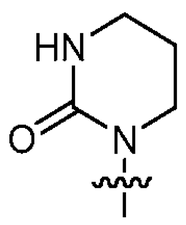
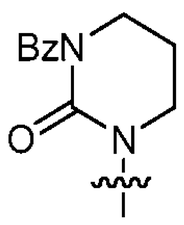
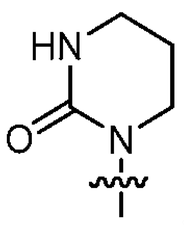
[00373] In some embodiments, X^1 is $-C(-)=$, and X^4 is $=C(-N(R^{B4})_2)-$. In some embodiments, two R groups on the same atom, e.g., a nitrogen atom, are taken together to form optionally substituted $=CH_2$ or =NH. In some embodiments, two R groups on the same atom, e.g., a nitrogen atom, are taken together to form optionally substituted $=C(-L^{B4}-R)_2$, $=N-L^{B4}-R$. In some embodiments, a formed group is $=CHN(R)_2$. In some embodiments, a formed group is $=CHN(CH_3)_2$. In some embodiments, X^4 is $=C(-N=CHN(CH_3)_2)-$. In some embodiments, $-N(R^{B4})_2$ is $-NR^{B4}$. In some embodiments, R^{B4} is $-NHC(O)R$. In some embodiments, Ring BA is optionally substituted or protected

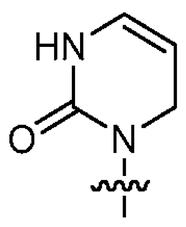
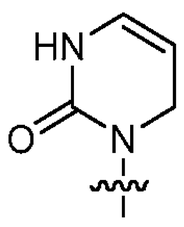
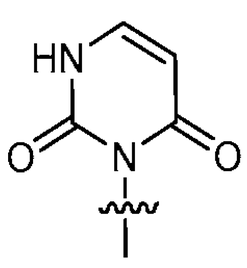
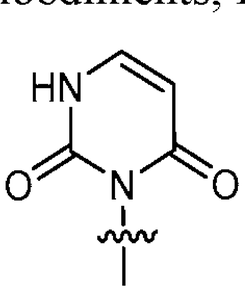
. In some embodiments, Ring BA is

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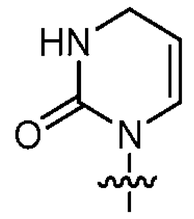
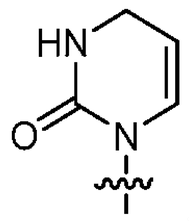
some embodiments, Ring BA is  .

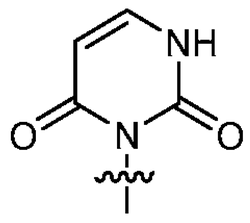
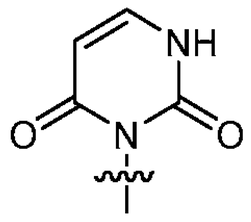
[00374] In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, and X^3 is $-N(R^{B3})-$. In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$, and X^4 is $-C(R^{B4})=$. In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$, X^4 is $-C(R^{B4})=$, and X^5 is $-C(R^{B5})=$. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  .

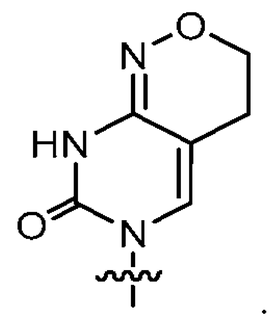
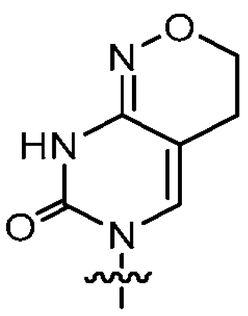
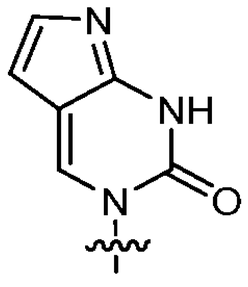
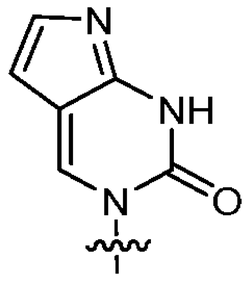
[00375] In some embodiments, X^3 is $-N(R')-$. In some embodiments, R' is $-C(O)R$. In some embodiments, X^4 is $-C(R^{B4})_2-$. In some embodiments, R^{B4} is $-R$. In some embodiments, R^{B4} is $-H$. In some embodiments, X^4 is $-CH_2-$. In some embodiments, X^5 is $-C(R^{B5})_2-$. In some embodiments, R^{B5} is $-R$. In some embodiments, R^{B5} is $-H$. In some embodiments, X^5 is $-CH_2-$. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is .

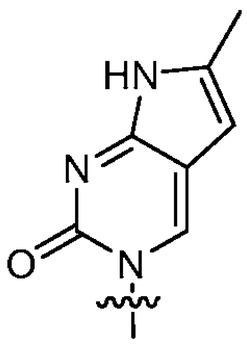
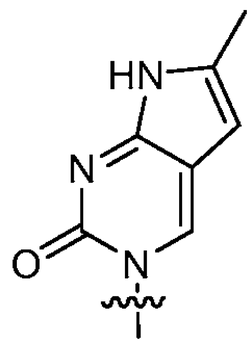
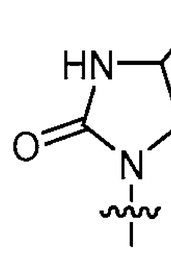
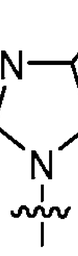
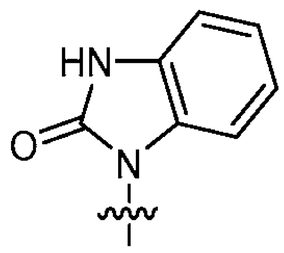
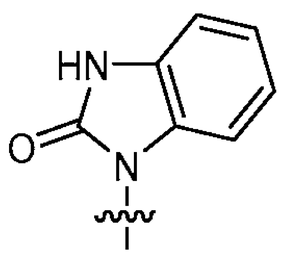
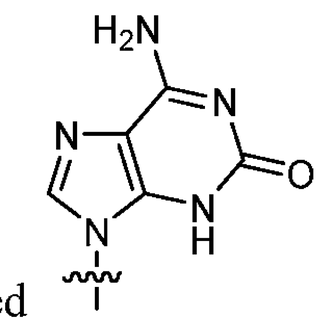
[00376] In some embodiments, X^4 is $-C(R^{B4})=$. In some embodiments, X^4 is $-CH=$. In some embodiments, X^5 is $-C(R^{B5})=$. In some embodiments, X^5 is $-CH=$. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  .

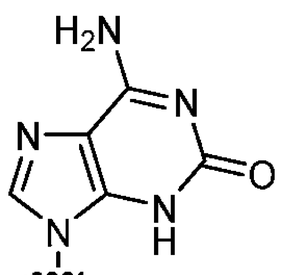
[00377] In some embodiments, X^4 is $-C(R^{B4})_2-$. In some embodiments, X^4 is $-CH_2-$. In some embodiments, X^5 is $-C(R^{B5})=$. In some embodiments, X^5 is $-CH=$. In some embodiments, Ring BA is

optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  .

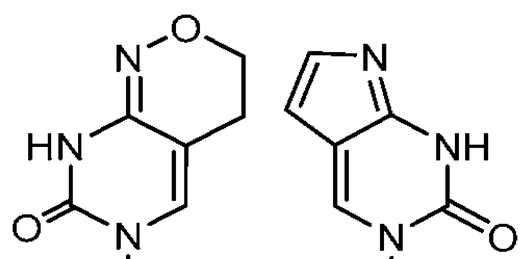
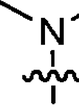
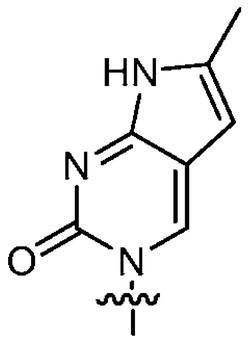
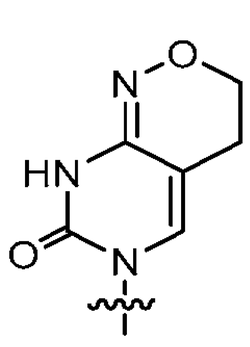
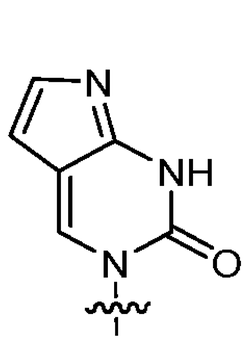
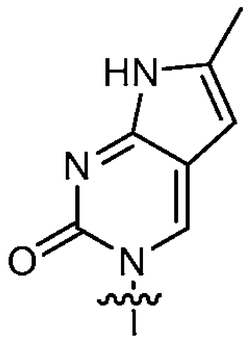
[00378] In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$, X^4 is $-C(R^{B4})=$, X^5 is $-C(R^{B5})=$, X^6 is $-C(O)-$. In some embodiments, each of R^{B3}, R^{B4} and R^{B5} is independently R. In some embodiments, R^{B3} is $-H$. In some embodiments, R^{B4} is $-H$. In some embodiments, R^{B5} is $-H$. In some embodiments, BA is or comprises optionally substituted or protected  . In some embodiments, BA is  .

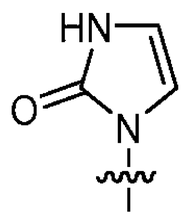
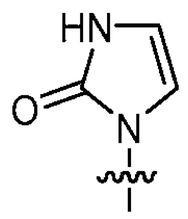
[00379] In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$. In some embodiments, X^4 is $-C(R^{B4})_2-$, wherein the two R^{B4} are taken together to form =O, or $=C(-L^{B4}-R^{B41})_2$, $=N-L^{B4}-R^{B41}$. In some embodiments, X^4 is $-C(=NR^{B4})-$. In some embodiments, X^5 is $-C(R^{B5})=$. In some embodiments, R^{B41} or R^{B4} and R^{B5} are R, and are taken together with their intervening atoms to form an optionally substituted ring as described herein. In some embodiment, Ring BA is optionally substituted or protected  . In some embodiment, Ring BA is  . In some embodiment, Ring BA is optionally substituted or protected  . In some embodiment, Ring BA is  . In some embodiments, X^1 is $-N(-)-$, X^2 is $-C(O)-$, X^3 is $-N=$. In some embodiments, X^4 is $-C(-N(R^{B4})_2)=$. In some embodiments, X^4 is $-C(-NHR^{B4})=$. In some embodiments, X^5 is $-C(R^{B5})=$. In some embodiments, one R^{B4} and R^{B5} are taken together to form an optionally substituted ring as described herein. In some embodiments, a formed ring is an optionally substituted 5-membered ring having a nitrogen atom. In some embodiment, Ring BA is optionally substituted

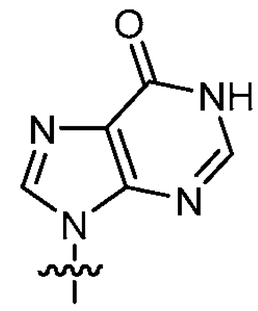
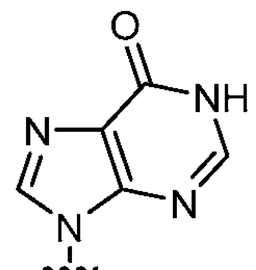
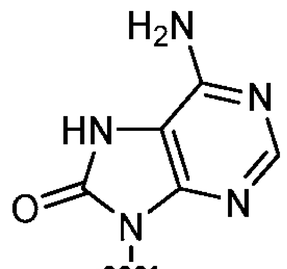
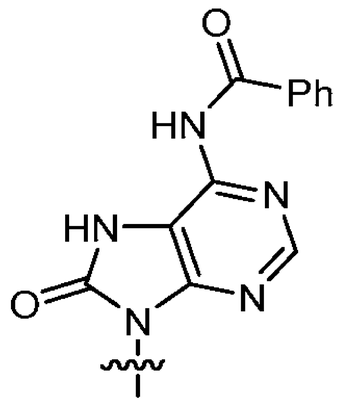
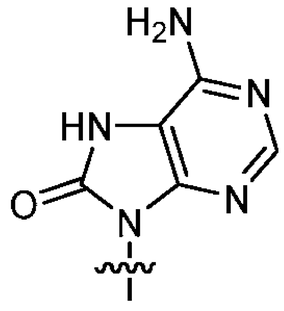
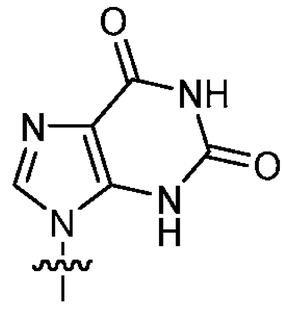
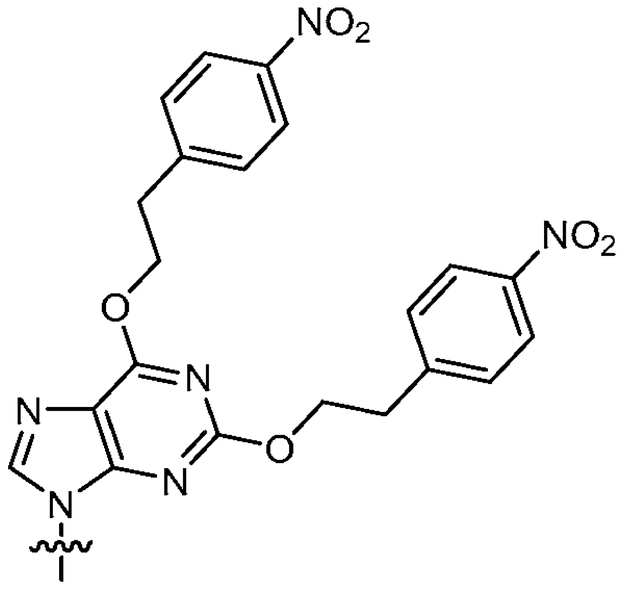
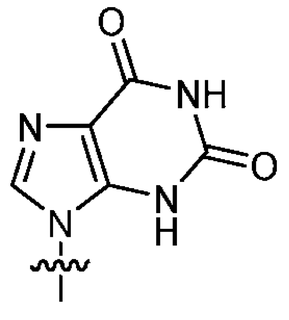
or protected  . In some embodiment, Ring BA is  . In some embodiment, Ring BA is optionally substituted or protected  . In some embodiment, Ring BA is  . In some embodiment, Ring BA is optionally substituted or protected  . In some embodiment, Ring BA is  . In some embodiment, Ring BA is optionally substituted or protected  .

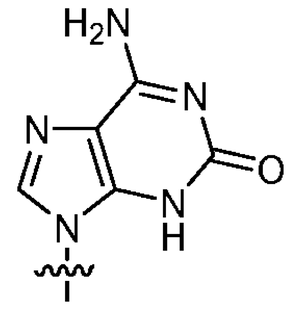
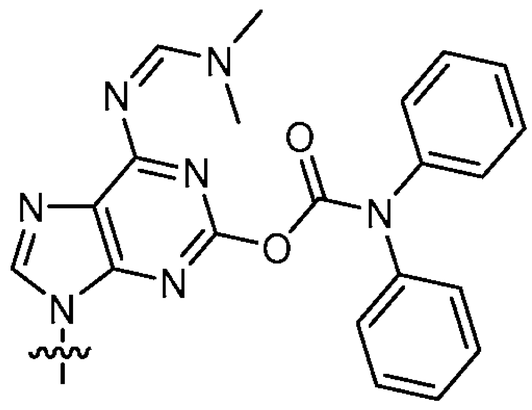
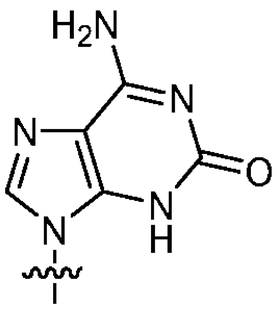
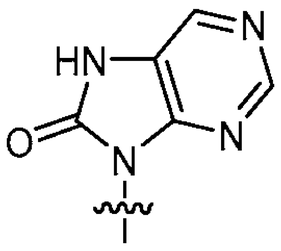
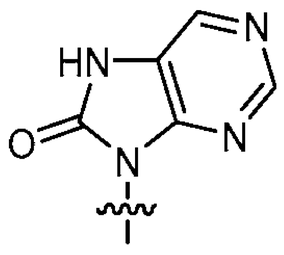
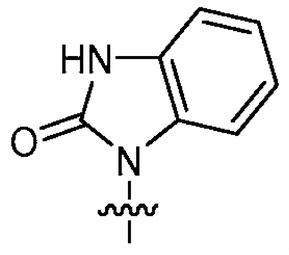
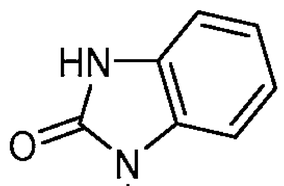
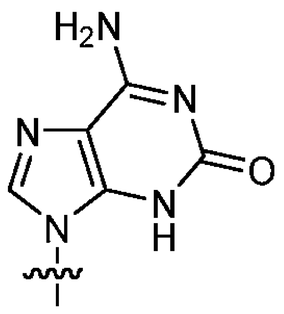
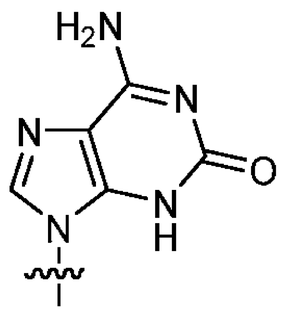
In some embodiment, Ring BA is  .

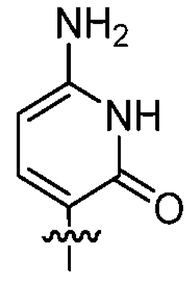
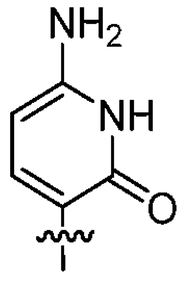
In some embodiment, Ring BA is  .

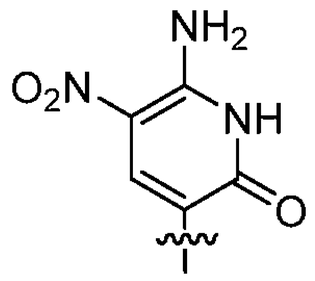
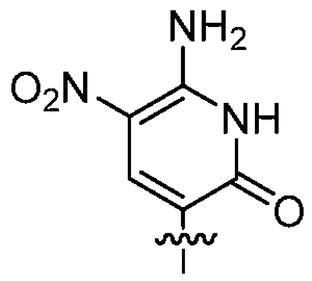
[00380] In some embodiments, Ring BA has the structure of formula BA-IV or BA-V. In some embodiments, X^1 is −N(−)−, X^2 is −C(O)−, and X^3 is −N=. In some embodiments, X^1 is −N(−)−, X^2 is −C(O)−, X^3 is −N=, and X^6 is −C(R^{B6})=. In some embodiments, Ring BA^A is 5-6 membered. In some embodiments, Ring BA^A is monocyclic. In some embodiments, Ring BA^A is partially unsaturated. In some embodiments, Ring BA^A is aromatic. In some embodiments, Ring BA^A has 0-2 heteroatoms. In some embodiments, Ring BA^A has 1-2 heteroatoms. In some embodiments, Ring BA^A has one heteroatom. In some embodiments, Ring BA^A has 2 heteroatoms. In some embodiments, a heteroatom is nitrogen. In some embodiments, heteroatom is oxygen. In some embodiments, Ring BA is optionally substituted or protected  , ,  , or  . In some embodiments, Ring BA is  ,  , or  .

[00381] In some embodiments, Ring BA is an optionally substituted 5-membered ring. In some embodiments, X^1 is bonded to X^5. In some embodiments, each of X^4 and X^5 is independently −CH=. In some embodiments, X^1 is −N(−)−, X^2 is −C(O)−, X^3 is −NH−, X^4 is −CH=, and X^5 is −CH=. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  .

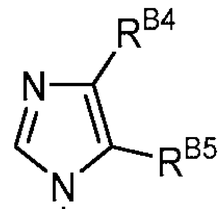
[00382] In some embodiments, Ring BA has the structure of formula BA-VI. In some embodiments, $X^{1'}$ is −N(−)−, $X^{2'}$ is −C(O)− and $X^{3'}$ is −N(R^{B3})−. In some embodiments, $X^{1'}$ is −N(−)−, $X^{2'}$ is −C(O)−, $X^{3'}$ is −N(R^{B3})−, $X^{4'}$ is −C($R^{B4'}$)=, $X^{5'}$ is −N=, $X^{6'}$ is −C($R^{B6'}$)=, and $X^{7'}$ is −N=. In some embodiments, $X^{1'}$ is −N(−)−, $X^{2'}$ is −C(O)−, $X^{3'}$ is −N(R^{B3})−, $X^{4'}$ is −C($R^{B4'}$)=, $X^{5'}$ is −C($R^{B5'}$)=, $X^{6'}$ is −C($R^{B6'}$)=, and $X^{7'}$ is −C($R^{B7'}$)=. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  . In some

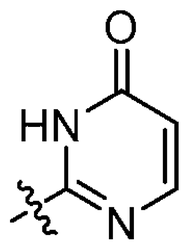
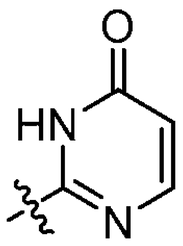
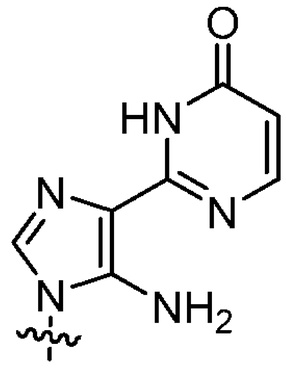
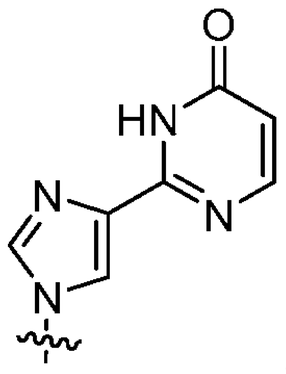
embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring BA is  . In some embodiments, $X^{1'}$ is $-N(-)-$, $X^{2'}$ is $-C(R^{B2'})=$, and $X^{3'}$ is $-N=$. In some embodiments, $X^{1'}$ is $-N(-)-$, $X^{2'}$ is $-C(R^{B2'})=$, $X^{3'}$ is $-N=$, $X^{4'}$ is $-C(-N(R^{B4'})_2)=$, $X^{5'}$ is $-N=$, $X^{6'}$ is $-C(O)-$, and $X^{7'}$ is $-N(R^{B7'})-$. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  .

[00383] In some embodiments, X^1 is $-C(-)=$, X^2 is $-C(O)-$, and X^3 is $-N(R^{B3})-$. In some embodiments, X^1 is $-C(-)=$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$, $-C(-N(R^{B4})_2)=$, and X^4 is $-C(R^{B4})=$. In some embodiments, X^1 is $-C(-)=$, X^2 is $-C(O)-$, X^3 is $-N(R^{B3})-$, $-C(-N(R^{B4})_2)=$, X^4 is $-C(R^{B4})=$, and X^6 is $-C(R^{B6})=$. In some embodiments, each of R^{B3}, R^{B4}, and R^{B6} is independently $-H$. In some embodiments, Ring BA is optionally substituted or protected  . In some embodiments, Ring BA is  . In some embodiments, Ring

BA is optionally substituted or protected  . In some embodiments, Ring BA is 

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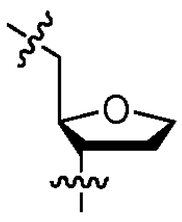
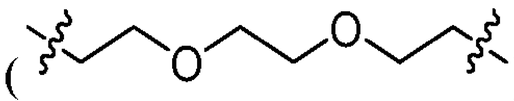
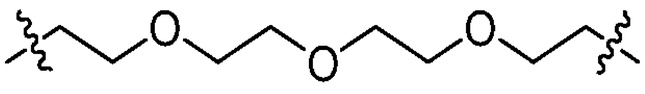
[00384] In some embodiments, Ring BA has the structure of  . In some embodiments, R^{B4} is optionally substituted aryl. In some embodiments, R^{B4} is optionally substituted  . In some embodiments, R^{B4} is  . In some embodiments, R^{B5} is −H. In some embodiments, R^{B5} is $-N(R')_2$. In some embodiments, R^{B5} is $-NH_2$. In some embodiments, Ring BA is  . In some embodiments, Ring BA is  .

[00385] As described herein, Ring BA may be optionally substituted. In some embodiments, each of X^2, X^3, X^4, X^5, X^6, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −CH=, −C(OH)=, $-C(-NH_2)=$, $-CH_2-$, −C(=NH)−, or −NH−. In some embodiments, each of X^2, X^3, X^4, X^5, X^6, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −CH=, $-CH_2-$, or −NH−. In some embodiments, each of X^2, X^3, X^4, X^5, X^6, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −CH=. In some embodiments, each of X^2, X^3, X^4, X^5, X^6, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is $-CH_2-$. In some embodiments, each of X^2, X^3, X^4, X^5, X^6, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −NH−. In some embodiments, X^2 is optionally substituted −CH=, −C(OH)=, $-C(-NH_2)=$, $-CH_2-$, −C(=NH)−, or −NH−. In some embodiments, X^3 is optionally substituted −CH=, −C(OH)=, $-C(-NH_2)=$, $-CH_2-$, −C(=NH)−, or −NH−.

In some embodiments, X^4 is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, X^5 is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, X^6 is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{2'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{3'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{4'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{5'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{6'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−. In some embodiments, $X^{7'}$ is optionally substituted −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−.

[00386] As demonstrated herein, in some embodiments provided oligonucleotides comprising certain nucleobases (e.g., b001A, b002A, b008U, C, A, etc.) opposite to target adenosines can among other things provide improved editing efficiency (e.g., compared to a reference nucleobase such as U). In some embodiments, an opposite nucleoside is linked to an I to its 3' side .

[00387] In some embodiments, a nucleobase is Ring BA as described herein. In some embodiments, an oligonucleotide comprises one or more Ring BA as described herein.

[00388] In some embodiments, an opposite nucleoside is abasic, e.g., having the structure of L010 (), L012 (), or L028 (). As appreciated by those skilled in the art and demonstrated in various oligonucleotides, abasic nucleosides may also be utilized in other portions of oligonucleotides, and oligonucleotides may comprise one or more (e.g., 1, 2, 3, 4, 5, or more), optionally consecutive, abasic nucleosides. In some embodiments, a first domain comprises one or more optionally consecutive, abasic nucleosides. In some embodiments, an oligonucleotide comprises one and no more than one abasic nucleoside. In some embodiments, each abasic nucleoside is independently in a first domain or a first subdomain of a second domain. In some embodiments, each abasic nucleoside is independently in a first domain. In some embodiments, each abasic nucleoside is independently in a first subdomain of a second domain. In some embodiments, an abasic nucleoside is opposite to a target adenosine. As demonstrated herein, a single abasic nucleoside may replace one or more nucleosides each of which independently comprises a nucleobase in a reference oligonucleotide, for example, L010 may be utilized to replace 1 nucleoside which comprises a nucleobase, L012 may be utilized to replace 1, 2 or 3 nucleosides each of which independently comprises a nucleobase, and L028 may be utilized to replace 1, 2 or 3 nucleosides each of which independently comprises a nucleobase. In some embodiments, a basic nucleoside is linked to its 3' immediate nucleoside (which is optionally abasic) through a stereorandom linkage (e.g., a stereorandom phosphorothioate internucleotidic linkage). In some embodiments, each basic nucleoside is independently

linked to its 3' immediate nucleoside (which is optionally abasic) through a stereorandom linkage (e.g., a stereorandom phosphorothioate internucleotidic linkage).

[00389] In some embodiments, a modified nucleobase opposite to a target adenine can greatly improve properties and/or activities of an oligonucleotide. In some embodiments, a modified nucleobase at the opposite position can provide high activities even when there is a G next to it (e.g., at the 3' side), and/or other nucleobases, e.g. C, provide much lower activities or virtually no detect activates.

[00390] In some embodiments, a second domain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars). In some embodiments, a second domain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a second domain comprises one or more modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar is a bicyclic sugar, e.g., a LNA sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar).

[00391] In some embodiments, a second domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars. In some embodiments, a second domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently bicyclic sugars (e.g., a LNA sugar) or a 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a second domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, the number is 6. In some embodiments, the number is 7. In some embodiments, the number is 8. In some embodiments, the number is 9. In some embodiments, the number is 10. In some embodiments, the number is 11. In some embodiments, the number is 12. In some embodiments, the number is 13. In some embodiments, the number is 14. In some embodiments, the number is 15. In some embodiments, the number is 16. In some embodiments, the number is 17. In some embodiments, the number is 18. In some embodiments, the number is 19. In some embodiments, the number is 20. In some embodiments, R is methyl.

[00392] In some embodiments, about 5%-100%, (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-

100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a second domain are independently a modified sugar. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a second domain are independently a bicyclic sugar (e.g., a LNA sugar) or a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a second domain are independently a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, R is methyl.

[00393] In some embodiments, a second domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a second domain are independently modified sugars with a modification that is not 2'-F. In some embodiments, about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%,

75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a second domain are independently modified sugars with a modification that is not 2'-F. In some embodiments, modified sugars of a second domain are each independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00394] In some embodiments, a second domain comprises one or more 2'-F modified sugars. In some embodiments, a second domain comprises no 2'-F modified sugars. In some embodiments, a second domain comprises one or more bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H. In some embodiments, levels of bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H, individually or combined, are relatively high compared to level of 2'-F modified sugars. In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a second domain comprises 2'-F. In some embodiments, no more than about 50% of sugars in a second domain comprises 2'-F. In some embodiments, a second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification. In some embodiments, a second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification. In some embodiments, a second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) bicyclic sugars, e.g., LNA sugars. In some embodiments, a second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

[00395] In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a second domain comprises 2'-MOE. In some embodiments, no more than about 50% of sugars in a second domain comprises 2'-MOE. In some embodiments, no sugars in a second domain comprises 2'-MOE.

[00396] In some embodiments, a second domain comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in a second domain are modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a second domain is independently a modified internucleotidic linkage. In some

embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a neutral internucleotidic linkage, e.g., n001. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a second domain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a second domain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a second domain is chirally controlled. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a second domain is *S*p. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) phosphorothioate internucleotidic linkages in a second domain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%,

75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a second domain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a second domain is *S*p. In some embodiments, the number is one or more. In some embodiments, the number is 2 or more. In some embodiments, the number is 3 or more. In some embodiments, the number is 4 or more. In some embodiments, the number is 5 or more. In some embodiments, the number is 6 or more. In some embodiments, the number is 7 or more. In some embodiments, the number is 8 or more. In some embodiments, the number is 9 or more. In some embodiments, the number is 10 or more. In some embodiments, the number is 11 or more. In some embodiments, the number is 12 or more. In some embodiments, the number is 13 or more. In some embodiments, the number is 14 or more. In some embodiments, the number is 15 or more. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, each internucleotidic linkage linking two second domain nucleosides is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage is independently a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage of a second domain is bonded to two nucleosides of the second domain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a first domain and a nucleoside in a second domain may be properly considered an internucleotidic linkage of a second domain. In some embodiments, it was observed that a high percentage (e.g., relative to *R*p internucleotidic linkages and/or natural phosphate linkages) of *S*p internucleotidic linkages provide improved properties and/or activities, e.g., high stability and/or high adenosine editing activity.

[00397] In some embodiments, a second domain comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in a second domain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in a second domain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in a second domain. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 1-5, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *R*p chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about

4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10.

[00398] In some embodiments, each phosphorothioate internucleotidic linkage in a second domain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a second domain is chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00399] In some embodiments, each phosphorothioate internucleotidic linkage in a second domain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a second domain is chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00400] In some embodiments, as illustrated in certain examples, a second domain comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in a second domain is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, it is about 1. In some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in a second domain are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of a second domain. In some embodiments, the last two or three or four internucleotidic linkages of a second domain comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In some embodiments, the last two or three or four internucleotidic linkages of a second domain comprise at least one internucleotidic linkage that is not n001.

[00401] In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second domain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second domain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second domain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second domain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second domain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the last two nucleosides of a second domain are the last two nucleosides of an oligonucleotide. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second domain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second domain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second domain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second domain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second domain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage such as n001.

[00402] In some embodiments, a second domain comprises one or more natural phosphate linkages. In some embodiments, a second domain contains no natural phosphate linkages.

[00403] In some embodiments, a second domain recruits, promotes or contribute to recruitment of, a protein such as an ADAR protein. In some embodiments, a second domain recruits, or promotes or contribute to interactions with, a protein such as an ADAR protein. In some embodiments, a second domain contacts with a RNA binding domain (RBD) of ADAR. In some embodiments, a second domain contacts with a catalytic domain of ADAR which has a deaminase activity. In some embodiments, various nucleobases, sugars and/or internucleotidic linkages may interact with one or more residues of proteins, e.g., ADAR proteins.

[00404] In some embodiments, a second domain comprises or consists of a first subdomain as described herein. In some embodiments, a second domain comprises or consists of a second subdomain as described herein. In some embodiments, a second domain comprises or consists of a third subdomain as described herein. In some embodiments, a second domain comprises or consists of a first subdomain, a second subdomain and a third subdomain from 5' to 3'. Certain embodiments of such subdomains are described below.

First Subdomains

[00405] As described herein, in some embodiment, an oligonucleotide comprises a first domain and a second domain from 5' to 3'. In some embodiments, a second domain comprises or consists of a first subdomain, a second subdomain, and a third subdomain from 5' to 3'. Certain embodiments of a first subdomain are described below as examples. In some embodiments, a first subdomain comprise a nucleoside

opposite to target adenosine to be modified (e.g., conversion to I).

[00406] In some embodiments, a first subdomain has a length of about 1-50, 1-40, 1-30, 1-20 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases. In some embodiments, a first subdomain has a length of about 5-30 nucleobases. In some embodiments, a first subdomain has a length of about 10-30 nucleobases. In some embodiments, a first subdomain has a length of about 10-20 nucleobases. In some embodiments, a first subdomain has a length of about 5-15 nucleobases. In some embodiments, a first subdomain has a length of about 13-16 nucleobases. In some embodiments, a first subdomain has a length of about 6-12 nucleobases. In some embodiments, a first subdomain has a length of about 6-9 nucleobases. In some embodiments, a first subdomain has a length of about 1-10 nucleobases. In some embodiments, a first subdomain has a length of about 1-7 nucleobases. In some embodiments, a first subdomain has a length of about 1-5 nucleobases. In some embodiments, a first subdomain has a length of about 1-3 nucleobases. In some embodiments, a first subdomain has a length of 1 nucleobase. In some embodiments, a first subdomain has a length of 2 nucleobases. In some embodiments, a first subdomain has a length of 3 nucleobases. In some embodiments, a first subdomain has a length of 4 nucleobases. In some embodiments, a first subdomain has a length of 5 nucleobases. In some embodiments, a first subdomain has a length of 6 nucleobases. In some embodiments, a first subdomain has a length of 7 nucleobases. In some embodiments, a first subdomain has a length of 8 nucleobases. In some embodiments, a first subdomain has a length of 9 nucleobases. In some embodiments, a first subdomain has a length of 10 nucleobases. In some embodiments, a first subdomain has a length of 11 nucleobases. In some embodiments, a first subdomain has a length of 12 nucleobases. In some embodiments, a first subdomain has a length of 13 nucleobases. In some embodiments, a first subdomain has a length of 14 nucleobases. In some embodiments, a first subdomain has a length of 15 nucleobases.

[00407] In some embodiments, a first subdomain is about, or at least about, 5-95%, 10%-90%, 20%-80%, 30%-70%, 40%-70%, 40%-60%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% of a second domain. In some embodiments, a percentage is about 30%-80%. In some embodiments, a percentage is about 30%-70%. In some embodiments, a percentage is about 40%-60%. In some embodiments, a percentage is about 20%. In some embodiments, a percentage is about 25%. In some embodiments, a percentage is about 30%. In some embodiments, a percentage is about 35%. In some embodiments, a percentage is about 40%. In some embodiments, a percentage is about 45%. In some embodiments, a percentage is about 50%. In some embodiments, a percentage is about 55%. In some embodiments, a percentage is about 60%. In some embodiments, a percentage is about 65%. In some embodiments, a percentage is about 70%. In some embodiments, a percentage is about 75%. In some embodiments, a percentage is about 80%. In some embodiments, a percentage is about 85%. In some embodiments, a percentage is about 90%.

[00408] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches exist

in a first subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches.

[00409] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles exist in a first subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 wobble. In some embodiments, there are 2 wobbles. In some embodiments, there are 3 wobbles. In some embodiments, there are 4 wobbles. In some embodiments, there are 5 wobbles. In some embodiments, there are 6 wobbles. In some embodiments, there are 7 wobbles. In some embodiments, there are 8 wobbles. In some embodiments, there are 9 wobbles. In some embodiments, there are 10 wobbles.

[00410] In some embodiments, duplexes of oligonucleotides and target nucleic acids in a first subdomain region comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

[00411] In some embodiments, a first subdomain is fully complementary to a target nucleic acid.

[00412] In some embodiments, a first subdomain comprises one or more modified nucleobases.

[00413] In some embodiments, a first subdomain comprise a nucleoside opposite to a target adenosine, e.g., when the oligonucleotide forms a duplex with a target nucleic acid. Suitable nucleobases including modified nucleobases in opposite nucleosides are described herein. For example, in some embodiment, an opposite nucleobase is optionally substituted or protected nucleobase selected from C, a tautomer of C, U, a tautomer of U, A, a tautomer of A, and a nucleobase which is or comprises Ring BA having the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA.

[00414] In some embodiments, a first subdomain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars). In some embodiments, a first subdomain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a first subdomain comprises one or more modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar is a bicyclic sugar, e.g., a LNA sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar).

[00415] In some embodiments, a first subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,

30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars. In some embodiments, a first subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently bicyclic sugars (e.g., a LNA sugar) or a 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a first subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, the number is 6. In some embodiments, the number is 7. In some embodiments, the number is 8. In some embodiments, the number is 9. In some embodiments, the number is 10. In some embodiments, the number is 11. In some embodiments, the number is 12. In some embodiments, the number is 13. In some embodiments, the number is 14. In some embodiments, the number is 15. In some embodiments, the number is 16. In some embodiments, the number is 17. In some embodiments, the number is 18. In some embodiments, the number is 19. In some embodiments, the number is 20. In some embodiments, R is methyl.

[00416] In some embodiments, about 5%-100%, (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a first subdomain are independently a modified sugar. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a first subdomain are independently a bicyclic sugar (e.g., a LNA sugar) or a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-

85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a first subdomain are independently a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, R is methyl.

[00417] In some embodiments, a first subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a first subdomain are independently modified sugars with a modification that is not 2'-F. In some embodiments, about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a first subdomain are independently modified sugars with a modification that is not 2'-F. In some embodiments, modified sugars of a first subdomain are each independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a first domain is a 2'-F modified sugar.

[00418] In some embodiments, a first subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some

embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a first subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a first subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00419] In some embodiments, each sugar in a first subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a first subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$. In some embodiments, each sugar in a first subdomain independently comprises 2'-OMe.

[00420] In some embodiments, a first subdomain comprises one or more 2'-F modified sugars. In some embodiments, a first subdomain comprises no 2'-F modified sugars. In some embodiments, a first subdomain comprises one or more bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H. In some embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-OMe modified sugars. In some embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) consecutive 2'-OMe modified sugars. In some embodiments, levels of bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H, individually or combined, are relatively high compared to level of 2'-F modified sugars. In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a first subdomain comprises 2'-F. In some embodiments, no more than about 50% of sugars in a first subdomain comprises 2'-F. In some embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification. In some embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification. In some

embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) bicyclic sugars, e.g., LNA sugars. In some embodiments, a first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

[00421] In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a first subdomain comprises 2'-MOE. In some embodiments, no more than about 50% of sugars in a first subdomain comprises 2'-MOE. In some embodiments, no sugars in a first subdomain comprises 2'-MOE.

[00422] In some embodiments, a first subdomain contains more 2'-OR modified sugars than 2'-F modified sugars. In some embodiments, each sugar in a first subdomain is independently a 2'-OR modified sugar or a 2'-F modified sugar. In some embodiments, a first subdomain contains only 3 nucleosides, two of which are independently 2'-OR modified sugars and one is a 2'-F modified sugar. In some embodiments, the 2'-F modified nucleoside is at the 3'-end of the first subdomain and connects to a second subdomain. In some embodiments, each 2'-OR modified sugar is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic, or a 2'–O–L^B–4' modification. In some embodiments, each 2'-OR modified sugar is independently 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE modified sugar. In some embodiments, a sugar is 2'-OMe modified and a sugar is 2'-MOE. In some embodiments, a first subdoman contains only 3 nucleosides which are N_2, N_3 and N_4.

[00423] In some embodiments, a first subdomain comprise about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in a first subdomain are modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a first subdomain is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified or chiral

internucleotidic linkage is a neutral internucleotidic linkage, e.g., n001. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a first subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a first subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a first subdomain is chirally controlled. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a first subdomain is *S*p. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) phosphorothioate internucleotidic linkages in a first subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a first subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-

100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a first subdomain is *S*p. In some embodiments, the number is one or more. In some embodiments, the number is 2 or more. In some embodiments, the number is 3 or more. In some embodiments, the number is 4 or more. In some embodiments, the number is 5 or more. In some embodiments, the number is 6 or more. In some embodiments, the number is 7 or more. In some embodiments, the number is 8 or more. In some embodiments, the number is 9 or more. In some embodiments, the number is 10 or more. In some embodiments, the number is 11 or more. In some embodiments, the number is 12 or more. In some embodiments, the number is 13 or more. In some embodiments, the number is 14 or more. In some embodiments, the number is 15 or more. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, each internucleotidic linkage linking two first subdomain nucleosides is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage is independently a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage of a first subdomain is bonded to two nucleosides of the first subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a first subdomain and a nucleoside in a second subdomain may be properly considered an internucleotidic linkage of a first subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a first subdomain and a nucleoside in a second subdomain is a modified internucleotidic linkage; in some embodiments, it is a chiral internucleotidic linkage; in some embodiments, it is chirally controlled; in some embodiments, it is *R*p; in some embodiments, it is *S*p.

[00424] In some embodiments, a first subdomain comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%,

65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in a first subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in a first subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in a first subdomain. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 1-5, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *Rp* chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about 4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some

embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10.

[00425] In some embodiments, each phosphorothioate internucleotidic linkage in a first subdomain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a first subdomain is chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00426] In some embodiments, as illustrated in certain examples, a first subdomain comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in a first subdomain is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, it is about 1. In some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in a first subdomain are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of a first subdomain. In some embodiments, the last two or three or four internucleotidic linkages of a first subdomain comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In some embodiments, the last two or three or four internucleotidic linkages of a first subdomain comprise at least one internucleotidic linkage that is not n001. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a first subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the

internucleotidic linkage linking the first two nucleosides of a first subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a first subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage such as n001.

[00427] In some embodiments, a first subdomain comprises one or more natural phosphate linkages. In some embodiments, a first subdomain contains no natural phosphate linkages. In some embodiments, one or more 2'-OR modified sugars wherein R is not –H are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-OMe modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, one or more 2'-MOE modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, each 2'-MOE modified sugar is independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-OR modified sugars wherein R is not –H are independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-OMe modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) 2'-MOE modified sugars are independently bonded to a natural phosphate linkage. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) internucleotidic linkages bonded to two 2'-OR modified sugars are independently natural phosphate linkages. In some embodiments, 50% or more (e.g., 50%-100%, 50%-90%, 50-80%, or about 50%, 60%, 66%, 70%, 75%, 80%, 90% or more) internucleotidic linkages bonded to two 2'-OMe or 2'-MOE modified sugars are independently natural phosphate linkages.

[00428] In some embodiments, a first subdomain comprises a 5'-end portion, e.g., one having a length of about 1-20, 1-15, 1-10, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a 5'-end portion has a length of about 3-6 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases. In some embodiments, a length is 6 nucleobases. In some embodiments, a length is 7 nucleobases. In some embodiments, a length is 8 nucleobases. In some embodiments, a length is 9 nucleobases. In some embodiments, a length is 10 nucleobases. In some embodiments, a 5'-end portion comprises the 5'-end

nucleobase of a first subdomain.

[00429] In some embodiments, a 5'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 5'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-20, 1-15, 1-10, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00430] In some embodiments, one or more of the modified sugars independently comprises 2'-F or 2'-OR, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, one or more of the modified sugars are independently 2'-F or 2'-OMe. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl.

[00431] In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are *R*p. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are *S*p. In some embodiments, each internucleotidic linkage of a 5'-end portion is *S*p.

[00432] In some embodiments, a 5'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) mismatches as described herein. In some embodiments, a 5'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) wobbles as described herein. In some

embodiments, a 5'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00433] In some embodiments, a first subdomain comprises a 3'-end portion, e.g., one having a length of about 1-20, 1-15, 1-10, 1-5, 1-3, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a 3'-end portion has a length of about 1-3 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases. In some embodiments, a length is 6 nucleobases. In some embodiments, a length is 7 nucleobases. In some embodiments, a length is 8 nucleobases. In some embodiments, a length is 9 nucleobases. In some embodiments, a length is 10 nucleobases. In some embodiments, a 3'-end portion comprises the 3'-end nucleobase of a first subdomain. In some embodiments, a first subdomain comprises or consists of a 5'-end portion and a 3'-end portion.

[00434] In some embodiments, a 5'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 5'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-20, 1-15, 1-10, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 3'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 3'-end portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00435] In some embodiments, one or more of the modified sugars independently comprises 2'-F or 2'-OR, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, one or more of the modified sugars are independently 2'-F or 2'-OMe. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a

sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl.

[00436] In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a higher level (in numbers and/or percentage) of 2'-F modified sugars and/or sugars comprising two 2'-H (e.g., natural DNA sugars), and/or a lower level (in numbers and/or percentage) of other types of modified sugars, e.g., bicyclic sugars and/or sugars with 2'-OR modifications wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a higher level of 2'-F modified sugars and/or a lower level of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a higher level of 2'-F modified sugars and/or a lower level of 2'-OMe modified sugars. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a lower level of 2'-F modified sugars and/or a higher level of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a lower level of 2'-F modified sugars and/or a higher level of 2'-OMe modified sugars. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a higher level of natural DNA sugars and/or a lower level of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 5'-end portion, a 3'-end portion contains a higher level of natural DNA sugars and/or a lower level of 2'-OMe modified sugars. In some embodiments, a 3'-end portion contains low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of modified sugars which are bicyclic sugars or sugars comprising 2'-OR wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl). In some embodiments, a 3'-end portion contains no modified sugars which are bicyclic sugars or sugars comprising 2'-OR wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl).

[00437] In some embodiments, one or more modified sugars independently comprise 2'-F. In some embodiments, no modified sugars comprises 2'-OMe or other 2'-OR modifications wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar of a 3'-end portion independently comprises two 2'-H or a 2'-F modification. In some embodiments, a 3'-end portion comprises 1, 2, 3, 4, or 5 2'-F modified sugars. In some embodiments, a 3'-end portion comprises 1-3 2'-F modified sugars. In some embodiments, a 3'-end portion comprises 1, 2, 3, 4, or 5 natural DNA sugars. In some embodiments, a 3'-end portion comprises 1-3 natural DNA sugars.

[00438] In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are *R*p. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion

are *S*p. In some embodiments, each internucleotidic linkage of a 3'-end portion is *S*p. In some embodiments, a 3'-end portion contains a higher level (in number and/or percentage) of *R*p internucleotidic linkage and/or natural phosphate linkage compared to a 5'-end portion.

[00439] In some embodiments, a 3'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) mismatches as described herein. In some embodiments, a 3'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) wobbles as described herein. In some embodiments, a 3'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00440] In some embodiments, a first subdomain recruits, promotes or contribute to recruitment of, a protein such as an ADAR protein, e.g., ADAR1, ADAR2, etc. In some embodiments, a first subdomain recruits, or promotes or contribute to interactions with, a protein such as an ADAR protein. In some embodiments, a first subdomain contacts with a RNA binding domain (RBD) of ADAR. In some embodiments, a first subdomain contacts with a catalytic domain of ADAR which has a deaminase activity. In some embodiments, a first subdomain contact with a domain that has a deaminase activity of ADAR1. In some embodiments, a first subdomain contact with a domain that has a deaminase activity of ADAR2. In some embodiments, various nucleobases, sugars and/or internucleotidic linkages of a first subdomain may interact with one or more residues of proteins, e.g., ADAR proteins.

Second Subdomains

[00441] As described herein, in some embodiment, an oligonucleotide comprises a first domain and a second domain from 5' to 3'. In some embodiments, a second domain comprises or consists of a first subdomain, a second subdomain, and a third subdomain from 5' to 3'. Certain embodiments of a second subdomain are described below as examples. In some embodiments, a second subdomain comprise a nucleoside opposite to a target adenosine to be modified (e.g., conversion to I). In some embodiments, a second subdomain comprises one and no more than one nucleoside opposite to a target adenosine. In some embodiments, each nucleoside opposite to a target adenosine of an oligonucleotide is in a second subdomain.

[00442] In some embodiments, a second subdomain has a length of about 1-10, 1-5, 1-3, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a second subdomain has a length of about 1-10 nucleobases. In some embodiments, a second subdomain has a length of about 1-5 nucleobases. In some embodiments, a second subdomain has a length of about 1-3 nucleobases. In some embodiments, a second subdomain has a length of 1 nucleobase. In some embodiments, a second subdomain has a length of 2 nucleobases. In some embodiments, a second subdomain has a length of 3 nucleobases. In some embodiments, all the nucleosides in a second subdomain are 5'-$N_1N_0N_{-1}$-3'.

[00443] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches exist in a second subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches.

[00444] In some embodiments, a second subdomain comprises one and no more than one mismatch. In some embodiments, a second subdomain comprises two and no more than two mismatches. In some embodiments, a second subdomain comprises two and no more than two mismatches, wherein one mismatch is between a target adenosine and its opposite nucleoside, and/or one mismatch is between a nucleoside next to a target adenosine and its corresponding nucleoside in an oligonucleotide. In some embodiments, a mismatch between a nucleoside next to a target adenosine and its corresponding nucleoside in an oligonucleotide is a wobble. In some embodiments, a wobble is I-C. In some embodiments, C is next to a target adenosine, e.g., immediately to its 3' side.

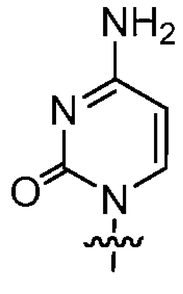
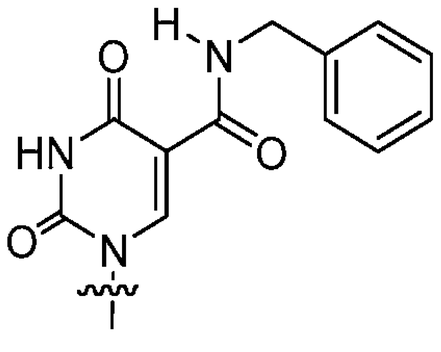
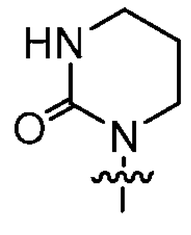
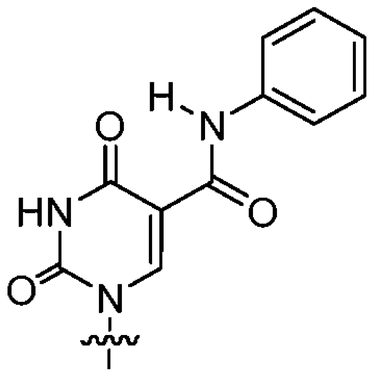
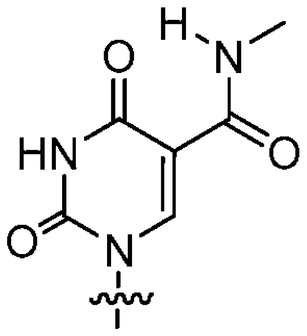
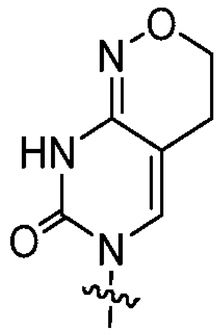
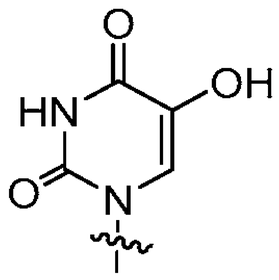
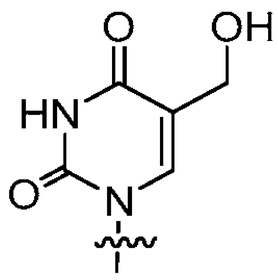
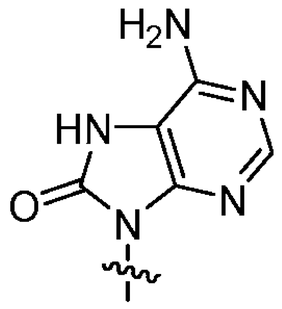
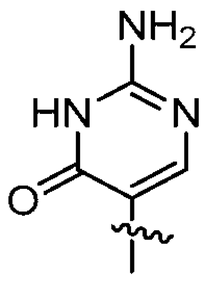
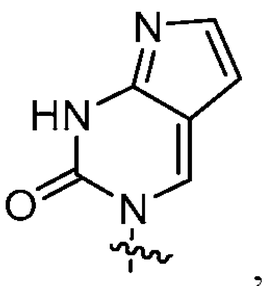
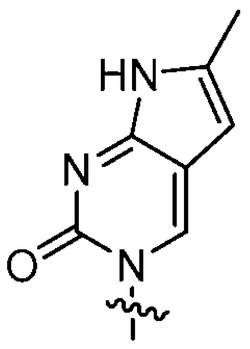
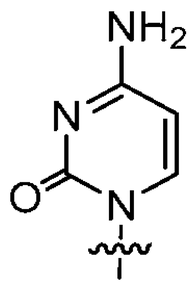
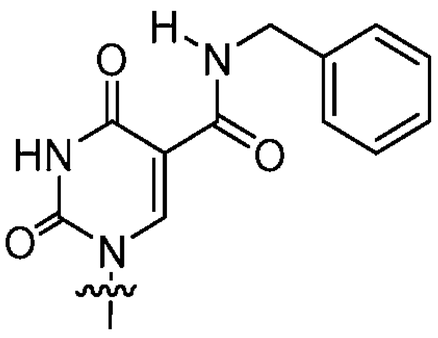
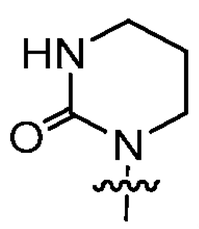
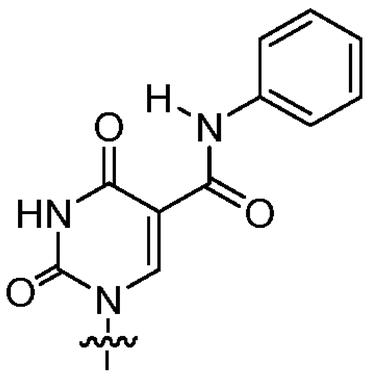
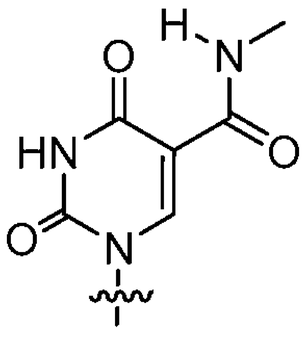
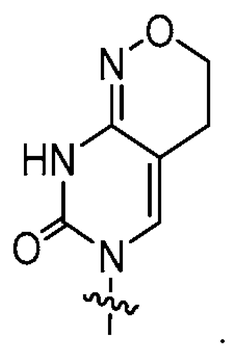
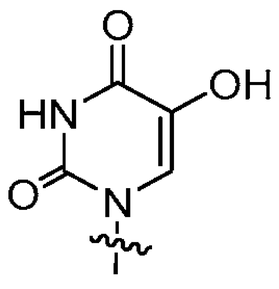
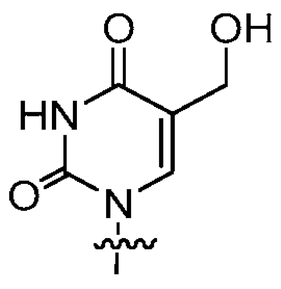
[00445] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles exist in a second subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 wobble. In some embodiments, there are 2 wobbles. In some embodiments, there are 3 wobbles. In some embodiments, there are 4 wobbles. In some embodiments, there are 5 wobbles. In some embodiments, there are 6 wobbles. In some embodiments, there are 7 wobbles. In some embodiments, there are 8 wobbles. In some embodiments, there are 9 wobbles. In some embodiments, there are 10 wobbles.

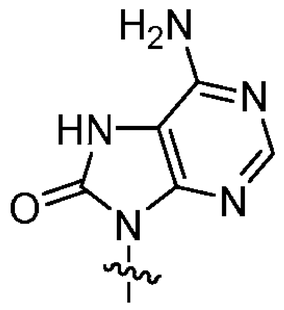
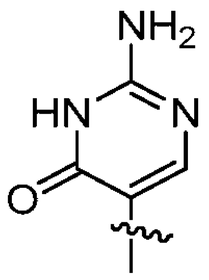
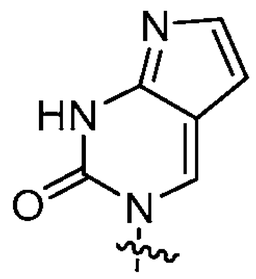
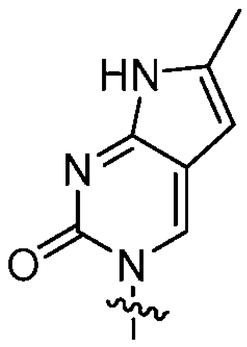
[00446] In some embodiments, duplexes of oligonucleotides and target nucleic acids in a second subdomain region comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

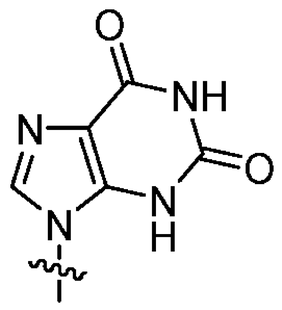
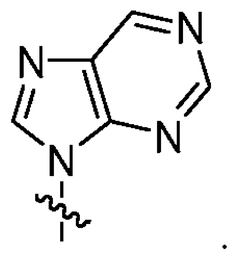
[00447] In some embodiments, a second subdomain is fully complementary to a target nucleic acid.

[00448] In some embodiments, a second subdomain comprises one or more modified nucleobases.

[00449] In some embodiments, a second subdomain comprise a nucleoside opposite to a target adenosine, e.g., when the oligonucleotide forms a duplex with a target nucleic acid. Suitable nucleobases including modified nucleobases in opposite nucleosides are described herein. For example, in some embodiment, an opposite nucleobase is optionally substituted or protected nucleobase selected from C, a tautomer of C, U, a tautomer of U, A, a tautomer of A, and a nucleobase which is or comprises Ring BA having the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-

V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA. For example, in some embodiments, an opposite nucleobase is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In

some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is  . In some embodiments, an opposite nucleobase is or  .

[00450] In some embodiments, a second subdomain comprises a modified nucleobase next to an opposite nucleobase. In some embodiments, it is to the 5' side. In some embodiments, it is to the 3' side. In some embodiments, on each side there is independently a modified nucleobase. Among other things, the present disclosure recognizes that nucleobases adjacent to (e.g., next to) opposite nucleobases may cause disruption (e.g., steric hindrance) to recognition, binding, interaction, and/or modification of target nucleic acids, oligonucleotides and/or duplexes thereof. In some embodiments, disruption is associated with an adjacent G. In some embodiments, the present disclosure provides nucleobases that can replace G and provide improved stability and/or activities compared to G. For example, in some embodiments, an adjacent nucleobase (e.g., 3'-immediate nucleoside of an opposite nucleoside) is hypoxanthine (replacing G to reduce disruption (e.g., steric hindrance) and/or forming wobble base pairing with C). In some embodiments, an adjacent nucleobase is a derivative of hypoxanthine. In some embodiments, 3'-immediate nucleoside comprises a nucleobase which is or comprise Ring BA having the structure of formula BA-VI. In some embodiments, an adjacent nucleobase is  . In some embodiments, an adjacent nucleobase is  .

[00451] In some embodiments, a second subdomain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars). In some embodiments, a second subdomain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a second subdomain comprises one or more modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a modified sugar is a bicyclic sugar, e.g., a LNA sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar). In some embodiments,

an opposite nucleoside comprises an acyclic sugar such as an UNA sugar. In some embodiments, such an acyclic sugar provides flexibility for proteins to perform modifications on a target adenosine.

[00452] In some embodiments, a second subdomain comprises about 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) modified sugars independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a second subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00453] In some embodiments, low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a second subdomain independently comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a second subdomain independently contains no 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted −CH_2−. In some embodiments, each sugar in a second subdomain independently contains no 2'-OMe.

[00454] In some embodiments, high levels (e.g., more than 50%, 60%, 70%, 80%, 90%, or 95%, 99%, or more than 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) of sugars in a second subdomain independently comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a second subdomain independently contains a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted −CH_2−. In some embodiments, each sugar in a second subdomain independently comprises 2'-OMe.

[00455] In some embodiments, a second subdomain comprises one or more 2'-F modified sugars.

[00456] In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a second subdomain are independently 2'-F modified sugars, sugars comprising two 2'-H (e.g., natural DNA sugars), or sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a second subdomain are independently 2'-F modified sugars, natural DNA sugars, or natural RNA sugars. In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a second subdomain are independently 2'-F modified sugars and natural DNA sugars. In some embodiments, a level is 100%. In some embodiments, a second subdomain comprise 1, 2, 3, 4 or 5 2'-F modified sugars. In some embodiments, a

second subdomain comprise 1, 2, 3, 4 or 5 sugars comprising two 2'-H. In some embodiments, a second subdomain comprise 1, 2, 3, 4 or 5 natural DNA sugars. In some embodiments, a second subdomain comprise 1, 2, 3, 4 or 5 sugars comprising 2'-OH. In some embodiments, a second subdomain comprise 1, 2, 3, 4 or 5 natural RNA sugars. In some embodiments, a number is 1. In some embodiments, a number is 2. In some embodiments, a number is 3. In some embodiments, a number is 4. In some embodiments, a number is 5.

[00457] In some embodiments, low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a second subdomain independently comprise a 2'-F modification. In some embodiments, each sugar in a second subdomain independently contains no 2'-F modification. In some embodiments, each sugar in a second subdomain independently contains no 2'-F.

[00458] In some embodiments, sugars of opposite nucleosides to target adenosines ("opposite sugars"), sugars of nucleosides 5'-next to opposite nucleosides ("5'-next sugars"), and/or sugars of nucleosides 3'-next to opposite nucleosides ("3-next sugars") are independently and optionally 2'-F modified sugars, sugars comprising two 2'-H (e.g., natural DNA sugars), or sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, an opposite sugar is a 2'-F modified sugar. In some embodiments, an opposite sugar is a sugar comprising two 2'-H. In some embodiments, an opposite sugar is a natural DNA sugar. In some embodiments, an opposite sugar is a sugar comprising 2'-OH. In some embodiments, an opposite sugar is a natural RNA sugar. For example, in some embodiments, each of a 5'-next sugar, an opposite sugar and a 3'-next sugar in an oligonucleotide is independently a natural DNA sugar. In some embodiments, a 5'-next sugar is a 2'-F modified sugar, and each of an opposite sugar and a 3'-next sugar is independently a natural DNA sugar.

[00459] In some embodiments, a 5'-next sugar is a 2'-F modified sugar. In some embodiments, a 5'-next sugar is a sugar comprising two 2'-H. In some embodiments, a 5'-next sugar is a natural DNA sugar. In some embodiments, a 5'-next sugar is a sugar comprising 2'-OH. In some embodiments, a 5'-next sugar is a natural RNA sugar.

[00460] In some embodiments, a 3'-next sugar is a 2'-F modified sugar. In some embodiments, a 3'-next sugar is a sugar comprising two 2'-H. In some embodiments, a 3'-next sugar is a natural DNA sugar. In some embodiments, a 3'-next sugar is a sugar comprising 2'-OH. In some embodiments, a 3'-next sugar is a natural RNA sugar.

[00461] In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a second subdomain comprises 2'-MOE. In some embodiments, no more than about 50% of sugars in a second subdomain comprises 2'-MOE. In some embodiments, no sugars in a second subdomain comprises 2'-MOE.

[00462] In some embodiments, a second subdomain comprise about 1-10 (e.g., about 1-5, 1-4, 1-3, about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) modified internucleotidic linkages. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-

80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in a second subdomain are modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a second subdomain is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a neutral internucleotidic linkage, e.g., n001. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, at least about 1-10 (e.g., about 1-5, 1-4, 1-3, about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) chiral internucleotidic linkages in a second subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a second subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a second subdomain is chirally controlled. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-10 (e.g., about 1-5, 1-4, 1-3, about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) chiral internucleotidic linkages in a second subdomain is *S*p. In some embodiments, at least about 1-10 (e.g., about 1-5, 1-4, 1-3, about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) phosphorothioate internucleotidic linkages in a second subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%,

70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a second subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a second subdomain is *S*p. In some embodiments, the number is one or more. In some embodiments, the number is 2 or more. In some embodiments, the number is 3 or more. In some embodiments, the number is 4 or more. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, each internucleotidic linkage linking two second subdomain nucleosides is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage is independently a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage of a second subdomain is bonded to two nucleosides of the second subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a second subdomain and a nucleoside in a first or third subdomain may be properly considered an internucleotidic linkage of a second subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a second subdomain and a nucleoside in a first or third subdomain is a modified internucleotidic linkage; in some embodiments, it is a chiral internucleotidic linkage; in some embodiments, it is chirally controlled; in some embodiments, it is *R*p; in some embodiments, it is *S*p.

[00463] In some embodiments, a second subdomain comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%,

70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in a second subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in a second subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in a second subdomain. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, 1-10 (e.g., about 1-5, 1-4, 1-3, about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages are independently *R*p chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about 4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10. In some embodiments, a second subdomain comprise a higher level (in number and/or percentage) of *R*p internucleotidic linkage compared to other portions (e.g., a first domain, a second domain overall, a first

subdomain, a third subdomain, or portions thereof). In some embodiments, a second subdomain comprise a higher level (in number and/or percentage) of *R*p internucleotidic linkage than *S*p internucleotidic linkage.

[00464] In some embodiments, each phosphorothioate internucleotidic linkage in a second subdomain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a second subdomain is chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00465] In some embodiments, each internucleotidic linkage bonded to a natural DNA or RNA or 2'-F modified sugar in a second subdomain is independently a modified internucleotidic linkage as described herein. In some embodiments, each such modified internucleotidic linkage is independently a phosphorothioate or non-negatively charged internucleotidic linkage such as a phosphoryl guanidine internucleotidic linkage like n001. In some embodiments, each such modified internucleotidic linkage is independently a phosphorothioate or n001 internucleotidic linkage. In some embodiments, each internucleotidic linkage bonded to two second subdomain nucleosides is independently a phosphorothioate internucleotidic linkage. In some embodiments, each phosphorothioate internucleotidic linkage bonded to two second subdomain nucleosides is independently chirally controlled and is *S*p. In some embodiments, one or more internucleotidic linkages bonded to a second subdomain nucleoside are independently non-negatively charged internucleotidic linkages such as phosphoryl guanidine internucleotidic linkages like n001. In some embodiments, an internucleotidic linkage bonded to N_{-1} and N_{-2} is an non-negatively charged internucleotidic linkage. In some embodiments, it is a phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is chirally controlled and is *R*p. In some embodiments, it is chirally controlled and is *S*p. In some embodiments, N_{-1} comprises hypoxanthine and in some embodiments, is deoxyinosine. In some embodiments, a phosphoryl guanidine internucleotidic linkage such as n001 bonded to 3' position of a nucleoside comprising hypoxanthine is chirally controlled and is *S*p. In some embodiments, oligonucleotides comprising such *S*p phosphoryl guanidine internucleotidic linkages such as *S*p n001 bonded to 3' position of nucleosides comprising hypoxanthine (e.g., deoxyinosine) provide various benefits, e.g., higher activities, better properties, lower manufacturing cost, and/or more readily available manufacturing materials, etc.

[00466] In some embodiments, as illustrated in certain examples, a second subdomain comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is

chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in a second subdomain is about 1-5, or about 1, 2, 3, 4, or 5. In some embodiments, it is about 1. In some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in a second subdomain are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of a second subdomain. In some embodiments, the last two or three or four internucleotidic linkages of a second subdomain comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In some embodiments, the last two or three or four internucleotidic linkages of a second subdomain comprise at least one internucleotidic linkage that is not n001. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a second subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a second subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last nucleoside of a second subdomain and the first nucleoside of a third subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last nucleoside of a second subdomain and the first nucleoside of a third subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last nucleoside of a second subdomain and the first nucleoside of a third subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last nucleoside of a second subdomain and the first nucleoside of a third subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last nucleoside of a second subdomain and the first nucleoside of a third

subdomain is a *Sp* phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage such as n001.

[00467] In some embodiments, a second subdomain comprises one or more natural phosphate linkages. In some embodiments, a second subdomain contains no natural phosphate linkages. In some embodiments, a second subdomain comprises at least 1 natural phosphate linkage. In some embodiments, a second subdomain comprises at least 2 natural phosphate linkages. In some embodiments, a second subdomain comprises at least 3 natural phosphate linkages. In some embodiments, a second subdomain comprises at least 4 natural phosphate linkages. In some embodiments, a second subdomain comprises at least 5 natural phosphate linkages.

[00468] In some embodiments, an opposite nucleoside is connected to its 5' immediate nucleoside through a natural phosphate linkage. In some embodiments, an opposite nucleoside is connected to its 5' immediate nucleoside through a natural phosphate linkage. In some embodiments, an opposite nucleoside is connected to its 5' immediate nucleoside through a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled. In some embodiments, a chiral internucleotidic linkage is *Rp*. In some embodiments, a chiral internucleotidic linkage is *Sp*.

[00469] In some embodiments, an opposite nucleoside is connected to its 3' immediate nucleoside (-1 position relative to the opposite nucleoside) through a natural phosphate linkage. In some embodiments, an opposite nucleoside is connected to its 3' immediate nucleoside through a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled. In some embodiments, a chiral internucleotidic linkage is *Rp*. In some embodiments, a chiral internucleotidic linkage is *Sp*. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *Sp*. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *Rp*. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *Rp*. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *Sp*. In some embodiments, a chiral

internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is not chirally controlled.

[00470] In some embodiments, a nucleoside at -1 position relative to an opposite nucleoside and a nucleoside at -2 position relative to an opposite nucleoside (e.g., in 5'-…$N_0N_{-1}N_{-2}$…3', if N_0 is an opposite nucleoside, N_{-1} is at -1 position and N_{-2} is at -2 position) is linked through a natural phosphate linkage. In some embodiments, they are connected through a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled. In some embodiments, a chiral internucleotidic linkage is *R*p. In some embodiments, a chiral internucleotidic linkage is *S*p. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *S*p. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *R*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *R*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *S*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is not chirally controlled.

[00471] In some embodiments, a nucleoside of a second subdomain and a nucleoside of a third subdomain is linked through a natural phosphate linkage. In some embodiments, they are connected through a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled. In some embodiments, a chiral internucleotidic linkage is *R*p. In some embodiments, a chiral internucleotidic linkage is *S*p. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *S*p. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage and is *R*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *R*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively

charged internucleotidic linkage (e.g., n001) and is chirally controlled and is *S*p. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage (e.g., n001) and is not chirally controlled.

[00472] In some embodiments, an oligonucleotide comprises 5'-$N_1N_0N_{-1}$–3', wherein each of N_1, N_0, and N_{-1} is independently a nucleoside, N_1 and N_0 bond to an internucleotidic linkage as described herein, and N_{-1} and N_0 bond to an internucleotidic linkage as described herein, and N_0 is opposite to a target adenosine. In some embodiments, the sugar of each of N_1, N_0, and N_{-1} is independently a natural DNA sugar or a 2'-F modified sugar. In some embodiments, the sugar of each of N_1, N_0, and N_{-1} is independently a natural DNA sugar. In some embodiments, the sugar of N_1 is a 2'-modified sugar, and the sugar of each of N_0 and N_{-1} is independently a natural DNA sugar. In some embodiments, such oligonucleotides provide high editing levels. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently *R*p. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently an *R*p phosphorothioate internucleotidic linkage. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently an *R*p phosphorothioate internucleotidic linkage, and each other phosphorothioate internucleotidic linkage in an oligonucleotide, if any, is independently *S*p. In some embodiments, a 5' internucleotidic linkage bonded to N_1 is *R*p. In some embodiments, an internucleotidic linkage bonded to N_1 and N_0 (i.e., a 3' internucleotidic linkage bonded to N_1) is *R*p. In some embodiments, an internucleotidic linkage bonded to N_{-1} and N_0 is *R*p. In some embodiments, a 3' internucleotidic linkage bonded to N_{-1} is *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 or N_1 is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 or N_{-1} is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_1 is independently *R*p. In some embodiments, each *R*p internucleotidic linkage is independently an *R*p phosphorothioate internucleotidic linkage. In some embodiments, each other chirally controlled phosphorothioate internucleotidic linkage in an oligonucleotide is independently *S*p.

[00473] In some embodiments, sugar of a 5' immediate nucleoside (e.g., N_1) is independently selected from a natural DNA sugar, a natural RNA sugar, and a 2'-F modified sugar (e.g., R^{2s} is –F). In some embodiments, sugar of an opposite nucleoside (e.g., N_0) is independently selected from a natural DNA sugar, a natural RNA sugar, and a 2'-F modified sugar. In some embodiments, sugar of a 3' immediate nucleoside (e.g., N_{-1}) is independently selected from a natural DNA sugar, a natural RNA sugar, and a 2'-F modified sugar. In some embodiments, sugars of a 5' immediate nucleoside, an opposite nucleoside, and a 3' immediate nucleoside are each independently a natural DNA sugar. In some embodiments, sugars of a 5' immediate nucleoside, an opposite nucleoside, and a 3' immediate nucleoside are a natural DNA sugar, a natural RNA sugar, and natural DNA sugar, respectively. In some embodiments, sugars of a 5' immediate nucleoside, an opposite nucleoside, and a 3' immediate nucleoside are a 2'-F modified sugar, a natural RNA sugar, and natural DNA sugar, respectively.

[00474] In some embodiments, sugar of an opposite nucleoside is a natural RNA sugar. In some

embodiments, such an opposite nucleoside is utilized with a 3' immediate I nucleoside (which is optionally complementary to a C in a target nucleic acid when aligned). In some embodiments, an internucleotidic linkage between the 3' immediate nucleoside (e.g., N_{-1}) and its 3' immediate nucleoside (e.g., N_{-2}) is a non-negatively charged internucleotidic linkage, e.g., n001. In some embodiments, it is stereorandom. In some embodiments, it is chirally controlled and is *R*p. In some embodiments, it is chirally controlled and is *S*p.

[00475] In some embodiments, an internucleotidic linkage that is bonded to a 3' immediate nucleoside (e.g., N_{-1}) and its 3' neighboring nucleoside (e.g., N_{-2} in 5'-$N_1N_0N_{-1}N_{-2}$–3') is a modified internucleotidic linkage. In some embodiments, it is a chiral internucleotidic linkage. In some embodiments, it is stereorandom. In some embodiments, it is a stereorandom phosphorothioate internucleotidic linkage. In some embodiments, it is a stereorandom non-negatively charged internucleotidic linkage. In some embodiments, it is stereorandom n001. In some embodiments, it is chirally controlled. In some embodiments, it is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is chirally controlled. In some embodiments, it is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, it is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001.

[00476] In some embodiments, N_{-1} is I. In some embodiments, I is utilized replacing G, e.g., when a target nucleic acid comprises 5'–CA–3' wherein A is a target adenosine. In some embodiments, 5'-$N_1N_0N_{-1}$–3'is 5'-N_1N_0I–3'. In some embodiments, N_0 is b001A, b002A, b003A, b008U, b001C, C, A, or U. In some embodiments, N_0 is b001A, b002A, b008U, b001C, C, or A. In some embodiments, N_0 is b001A, b002A, b008U, or b001C. In some embodiments, N_0 is b001A. In some embodiments, N_0 is b002A. In some embodiments, N_0 is b003A. In some embodiments, N_0 is b008U. In some embodiments, N_0 is b001C. In some embodiments, N_0 is A. In some embodiments, N_0 is U.

[00477] As demonstrated herein, in some embodiments provided oligonucleotides comprising certain nucleobases (e.g., b001A, b002A, b008U, C, A, etc.) opposite to target adenosines can among other things provide improved editing efficiency (e.g., compared to a reference nucleobase such as U). In some embodiments, an opposite nucleoside is linked to an I to its 3' side.

[00478] In some embodiments, a second subdomain comprises an editing region as described herein.

[00479] In some embodiments, a second subdomain comprises a 5'-end portion, e.g., one having a length of about 1-5, 1-3, or 1, 2, 3, 4, or 5 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases.

[00480] In some embodiments, a 5'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 5'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-5, 1-3, or 1, 2, 3, 4, or 5) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g.,

about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00481] In some embodiments, low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 5'-end portion independently comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a 5'-end portion independently contains no 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$. In some embodiments, each sugar in a 5'-end portion independently contains no 2'-OMe.

[00482] In some embodiments, a 5'-end portion comprises one or more 2'-F modified sugars.

[00483] In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 5'-end are independently 2'-F modified sugars, sugars comprising two 2'-H (e.g., natural DNA sugars), or sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 5'-end portion are independently 2'-F modified sugars, natural DNA sugars, or natural RNA sugars. In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 5'-end portion are independently 2'-F modified sugars and natural DNA sugars. In some embodiments, a level is 100%. In some embodiments, sugars of a 5'-end portion are selected from sugars having two 2'-H (e.g., natural DNA sugar) and 2'-F modified sugars. In some embodiments, a 5'-end portion comprise 1, 2, 3, 4 or 5 2'-F modified sugars. In some embodiments, a 5'-end portion comprise 1, 2, 3, 4 or 5 sugars comprising two 2'-H. In some embodiments, a 5'-end portion comprise 1, 2, 3, 4 or 5 natural DNA sugars. In some embodiments, a 5'-end portion comprise 1, 2, 3, 4 or 5 sugars comprising 2'-OH. In some embodiments, a 5'-end portion comprise 1, 2, 3, 4 or 5 natural RNA sugars. In some embodiments, a number is 1. In some embodiments, a number is 2. In some embodiments, a number is 3. In some embodiments, a number is 4. In some embodiments, a number is 5.

[00484] In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end

portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are *R*p. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are *S*p. In some embodiments, each internucleotidic linkage of a 5'-end portion is *S*p.

[00485] In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are *R*p. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 5'-end portion are *R*p. In some embodiments, each internucleotidic linkage of a 5'-end portion is *R*p.

[00486] In some embodiments, a 5'-end portion comprises one or more (e.g., about 1, 2, 3, 4, or 5) mismatches as described herein. In some embodiments, a 5'-end portion comprises one or more (e.g., about 1, 2, 3, 4, or 5) wobbles as described herein. In some embodiments, a 5'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00487] In some embodiments, a 5'-end portion comprises a nucleoside 5' next to an opposite nucleoside. In some embodiments, a nucleoside 5' next to an opposite nucleoside comprise a nucleobase as described herein.

[00488] In some embodiments, a second subdomain comprises a 3'-end portion, e.g., one having a length of about 1-5, 1-3, or 1, 2, 3, 4, or 5 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases. In some embodiments, a second subdomain consists a 5'-end portion and a 3'-end portion.

[00489] In some embodiments, a 3'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 3'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-5, 1-3, or 1, 2, 3, 4, or 5) of sugars in a 3'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 3'-end

portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00490] In some embodiments, low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 3'-end portion independently comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a 3'-end portion independently contains no 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$. In some embodiments, each sugar in a 3'-end portion independently contains no 2'-OMe.

[00491] In some embodiments, a 3'-end portion comprises one or more 2'-F modified sugars.

[00492] In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 3'-end are independently 2'-F modified sugars, sugars comprising two 2'-H (e.g., natural DNA sugars), or sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 3'-end portion are independently 2'-F modified sugars, natural DNA sugars, or natural RNA sugars. In some embodiments, a high level (e.g., about 60-100%, or about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more, or 100%) or all sugars in a 3'-end portion are independently 2'-F modified sugars and natural DNA sugars. In some embodiments, a level is 100%. In some embodiments, sugars of a 3'-end portion are selected from sugars having two 2'-H (e.g., natural DNA sugar) and 2'-F modified sugars. In some embodiments, a 3'-end portion comprise 1, 2, 3, 4 or 5 2'-F modified sugars. In some embodiments, a 3'-end portion comprise 1, 2, 3, 4 or 5 sugars comprising two 2'-H. In some embodiments, a 3'-end portion comprise 1, 2, 3, 4 or 5 natural DNA sugars. In some embodiments, a 3'-end portion comprise 1, 2, 3, 4 or 5 sugars comprising 2'-OH. In some embodiments, a 3'-end portion comprise 1, 2, 3, 4 or 5 natural RNA sugars. In some embodiments, a number is 1. In some embodiments, a number is 2. In some embodiments, a number is 3. In some embodiments, a number is 4. In some embodiments, a number is 5.

[00493] In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are *R*p. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are *S*p. In some embodiments, each internucleotidic linkage of a 3'-end portion is *S*p.

[00494] In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-

end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are *R*p. In some embodiments, one or more (e.g., about 1, 2, 3, 4, or 5) internucleotidic linkages of a 3'-end portion are *R*p. In some embodiments, each internucleotidic linkage of a 3'-end portion is *R*p.

[00495] In some embodiments, a 3'-end portion comprises one or more (e.g., about 1, 2, 3, 4, or 5) mismatches as described herein. In some embodiments, a 3'-end portion comprises one or more (e.g., about 1, 2, 3, 4, or 5) wobbles as described herein. In some embodiments, a 3'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00496] In some embodiments, a 3'-end portion comprises a nucleoside 3' next to an opposite nucleoside. In some embodiments, a nucleoside 3' next to an opposite nucleoside comprise a nucleobase as described herein. In some embodiments, a nucleoside 3' next to an opposite nucleoside forms a wobble pair with a corresponding nucleoside in a target nucleic acid. In some embodiments, the nucleobase of a nucleoside 3' next to an opposite nucleoside is hypoxanthine; in some embodiments, it is a derivative of hypoxanthine.

[00497] In some embodiments, a second subdomain recruits, promotes or contribute to recruitment of, a protein such as an ADAR protein, e.g., ADAR1, ADAR2, etc. In some embodiments, a second subdomain recruits, or promotes or contribute to interactions with, a protein such as an ADAR protein. In some embodiments, a second subdomain contacts with a RNA binding domain (RBD) of ADAR. In some embodiments, a second subdomain contacts with a catalytic domain of ADAR which has a deaminase activity. In some embodiments, a second subdomain contact with a domain that has a deaminase activity of ADAR1. In some embodiments, a second subdomain contact with a domain that has a deaminase activity of ADAR2. In some embodiments, various nucleobases, sugars and/or internucleotidic linkages of a second subdomain may interact with one or more residues of proteins, e.g., ADAR proteins.

Third Subdomains

[00498] As described herein, in some embodiment, an oligonucleotide comprises a first domain and a second domain from 5' to 3'. In some embodiments, a second domain comprises or consists of a first subdomain, a second subdomain, and a third subdomain from 5' to 3'. Certain embodiments of a third subdomain are described below as examples.

[00499] In some embodiments, a third subdomain has a length of about 1-50, 1-40, 1-30, 1-20 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50,

or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases. In some embodiments, a third subdomain has a length of about 5-30 nucleobases. In some embodiments, a third subdomain has a length of about 10-30 nucleobases. In some embodiments, a third subdomain has a length of about 10-20 nucleobases. In some embodiments, a third subdomain has a length of about 5-15 nucleobases. In some embodiments, a third subdomain has a length of about 13-16 nucleobases. In some embodiments, a third subdomain has a length of about 6-12 nucleobases. In some embodiments, a third subdomain has a length of about 6-9 nucleobases. In some embodiments, a third subdomain has a length of about 1-10 nucleobases. In some embodiments, a third subdomain has a length of about 1-7 nucleobases. In some embodiments, a third subdomain has a length of 1 nucleobase. In some embodiments, a third subdomain has a length of 2 nucleobases. In some embodiments, a third subdomain has a length of 3 nucleobases. In some embodiments, a third subdomain has a length of 4 nucleobases. In some embodiments, a third subdomain has a length of 5 nucleobases. In some embodiments, a third subdomain has a length of 6 nucleobases. In some embodiments, a third subdomain has a length of 7 nucleobases. In some embodiments, a third subdomain has a length of 8 nucleobases. In some embodiments, a third subdomain has a length of 9 nucleobases. In some embodiments, a third subdomain has a length of 10 nucleobases. In some embodiments, a third subdomain has a length of 11 nucleobases. In some embodiments, a third subdomain has a length of 12 nucleobases. In some embodiments, a third subdomain has a length of 13 nucleobases. In some embodiments, a third subdomain has a length of 14 nucleobases. In some embodiments, a third subdomain has a length of 15 nucleobases. In some embodiments, a third subdomain is shorter than a first subdomain. In some embodiments, a third subdomain is shorter than a first domain. In some embodiments, a third subdomain comprises a 3'-end nucleobase of a second domain.

[00500] In some embodiments, a third subdomain is about, or at least about, 5-95%, 10%-90%, 20%-80%, 30%-70%, 40%-70%, 40%-60%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% of a second domain. In some embodiments, a percentage is about 30%-80%. In some embodiments, a percentage is about 30%-70%. In some embodiments, a percentage is about 40%-60%. In some embodiments, a percentage is about 20%. In some embodiments, a percentage is about 25%. In some embodiments, a percentage is about 30%. In some embodiments, a percentage is about 35%. In some embodiments, a percentage is about 40%. In some embodiments, a percentage is about 45%. In some embodiments, a percentage is about 50%. In some embodiments, a percentage is about 55%. In some embodiments, a percentage is about 60%. In some embodiments, a percentage is about 65%. In some embodiments, a percentage is about 70%. In some embodiments, a percentage is about 75%. In some embodiments, a percentage is about 80%. In some embodiments, a percentage is about 85%. In some embodiments, a percentage is about 90%. In some embodiments, the 5'-end nucleoside of a third subdomain is N_{-2}. In some embodiments, all nucleosides from N_{-2} to the 3'-end are in a third subdomain.

[00501] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches exist in a third subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In

some embodiments, there is 1 mismatch. In some embodiments, there are 2 mismatches. In some embodiments, there are 3 mismatches. In some embodiments, there are 4 mismatches. In some embodiments, there are 5 mismatches. In some embodiments, there are 6 mismatches. In some embodiments, there are 7 mismatches. In some embodiments, there are 8 mismatches. In some embodiments, there are 9 mismatches. In some embodiments, there are 10 mismatches.

[00502] In some embodiments, one or more (e.g., 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobbles exist in a third subdomain when an oligonucleotide is aligned with a target nucleic acid for complementarity. In some embodiments, there is 1 wobble. In some embodiments, there are 2 wobbles. In some embodiments, there are 3 wobbles. In some embodiments, there are 4 wobbles. In some embodiments, there are 5 wobbles. In some embodiments, there are 6 wobbles. In some embodiments, there are 7 wobbles. In some embodiments, there are 8 wobbles. In some embodiments, there are 9 wobbles. In some embodiments, there are 10 wobbles.

[00503] In some embodiments, duplexes of oligonucleotides and target nucleic acids in a third subdomain region comprise one or more bulges each of which independently comprise one or more mismatches that are not wobbles. In some embodiments, there are 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges. In some embodiments, the number is 0. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5.

[00504] In some embodiments, a third subdomain is fully complementary to a target nucleic acid.

[00505] In some embodiments, a third subdomain comprises one or more modified nucleobases.

[00506] In some embodiments, a third subdomain comprises a nucleoside opposite to a target adenosine (an opposite nucleoside). In some embodiments, a third subdomain comprises a nucleoside 3' next to an opposite nucleoside. In some embodiments, a third subdomain comprises a nucleoside 5' next to an opposite nucleoside. Various suitable opposite nucleosides, including sugars and nucleobases thereof, have been described herein.

[00507] In some embodiments, a third subdomain comprise a nucleoside opposite to a target adenosine, e.g., when the oligonucleotide forms a duplex with a target nucleic acid. Suitable nucleobases including modified nucleobases in opposite nucleosides are described herein. For example, in some embodiment, an opposite nucleobase is optionally substituted or protected nucleobase selected from C, a tautomer of C, U, a tautomer of U, A, a tautomer of A, and a nucleobase which is or comprises Ring BA having the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA.

[00508] In some embodiments, a third subdomain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars). In some embodiments, a third subdomain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars). In some embodiments, a third subdomain comprises one or more modified sugars. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, a

modified sugar is a bicyclic sugar, e.g., a LNA sugar. In some embodiments, a modified sugar is an acyclic sugar (e.g., by breaking a C2-C3 bond of a corresponding cyclic sugar).

[00509] In some embodiments, a third subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars. In some embodiments, a third subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently bicyclic sugars (e.g., a LNA sugar) or a 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a third subdomain comprises about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars which are independently 2'-OR modified sugars, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, the number is 1. In some embodiments, the number is 2. In some embodiments, the number is 3. In some embodiments, the number is 4. In some embodiments, the number is 5. In some embodiments, the number is 6. In some embodiments, the number is 7. In some embodiments, the number is 8. In some embodiments, the number is 9. In some embodiments, the number is 10. In some embodiments, the number is 11. In some embodiments, the number is 12. In some embodiments, the number is 13. In some embodiments, the number is 14. In some embodiments, the number is 15. In some embodiments, the number is 16. In some embodiments, the number is 17. In some embodiments, the number is 18. In some embodiments, the number is 19. In some embodiments, the number is 20. In some embodiments, R is methyl.

[00510] In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising 2'-OH. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising two 2'-H. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) RNA sugars. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) DNA sugars.

[00511] In some embodiments, about 5%-100%, (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%,

85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a third subdomain are independently a modified sugar. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a third subdomain are independently a bicyclic sugar (e.g., a LNA sugar) or a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all sugars in a third subdomain are independently a 2'-OR modified sugar, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, R is methyl. In some embodiments, N_{-2} comprises a 2'-OR modified sugar wherein R is not −H. In some embodiments, N_{-3} comprises a 2'-F modified sugar. In some embodiments, each nucleoside after N_{-3} independently comprises a 2'-OR modified sugar wherein R is not −H. In some embodiments, N_{-3} comprises a 2'-F modified sugar and each other nucleosides in a third subdomain independently comprises a 2'-OR modified sugar wherein R is not −H. In some embodiments, a 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar.

[00512] In some embodiments, a third subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,

13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a third subdomain are independently modified sugars with a modification that is not 2'-F. In some embodiments, about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a third subdomain are independently modified sugars with a modification that is not 2'-F. In some embodiments, modified sugars of a third subdomain are each independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00513] In some embodiments, a third subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a third subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a third subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a

sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00514] In some embodiments, each sugar in a third subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification. In some embodiments, each sugar in a third subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$. In some embodiments, each sugar in a third subdomain independently comprises 2'-OMe.

[00515] In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F modified sugars. In some embodiments, a third subdomain comprises no 2'-F modified sugars. In some embodiments, a third subdomain comprises one or more bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H. In some embodiments, levels of bicyclic sugars and/or 2'-OR modified sugars wherein R is not –H, individually or combined, are relatively high compared to level of 2'-F modified sugars. In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a third subdomain comprises 2'-F. In some embodiments, no more than about 50% of sugars in a third subdomain comprises 2'-F. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) bicyclic sugars, e.g., LNA sugars. In some embodiments, a third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

[00516] In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in a third subdomain comprises 2'-MOE. In some embodiments, no more than about 50% of sugars in a third subdomain comprises 2'-MOE. In some embodiments, no sugars in a third subdomain comprises 2'-MOE.

[00517] In some embodiments, a third subdomain comprise about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%,

95%, or 100%, etc.) of internucleotidic linkages in a third subdomain are modified internucleotidic linkages. In some embodiments, each internucleotidic linkage in a third subdomain is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified or chiral internucleotidic linkage is a neutral internucleotidic linkage, e.g., n001. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a third subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a third subdomain is chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a third subdomain is chirally controlled. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in a third subdomain is *S*p. In some embodiments, each is independently chirally controlled. In some embodiments, at least about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) phosphorothioate internucleotidic

linkages in a third subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in a third subdomain is *S*p. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of phosphorothioate internucleotidic linkages in a third subdomain is *S*p. In some embodiments, the number is one or more. In some embodiments, the number is 2 or more. In some embodiments, the number is 3 or more. In some embodiments, the number is 4 or more. In some embodiments, the number is 5 or more. In some embodiments, the number is 6 or more. In some embodiments, the number is 7 or more. In some embodiments, the number is 8 or more. In some embodiments, the number is 9 or more. In some embodiments, the number is 10 or more. In some embodiments, the number is 11 or more. In some embodiments, the number is 12 or more. In some embodiments, the number is 13 or more. In some embodiments, the number is 14 or more. In some embodiments, the number is 15 or more. In some embodiments, a percentage is at least about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, each internucleotidic linkage linking two third subdomain nucleosides is independently a modified internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage is independently a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p chiral internucleotidic linkage. In some embodiments, each modified internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, each chiral internucleotidic linkages is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage of a third subdomain is bonded to two nucleosides of the third subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a third subdomain and a nucleoside in a second subdomain may be properly considered an

internucleotidic linkage of a third subdomain. In some embodiments, an internucleotidic linkage bonded to a nucleoside in a third subdomain and a nucleoside in a second subdomain is a modified internucleotidic linkage; in some embodiments, it is a chiral internucleotidic linkage; in some embodiments, it is chirally controlled; in some embodiments, it is *R*p; in some embodiments, it is *S*p.

[00518] In some embodiments, a third subdomain comprises a certain level of *R*p internucleotidic linkages. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all internucleotidic linkages in a third subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chiral internucleotidic linkages in a third subdomain. In some embodiments, a level is about e.g., about 5%-100%, about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc. of all chirally controlled internucleotidic linkages in a third subdomain. In some embodiments, a percentage is about or no more than about 50%. In some embodiments, a percentage is at least about 55%. In some embodiments, a percentage is at least about 60%. In some embodiments, a percentage is at least about 65%. In some embodiments, a percentage is at least about 70%. In some embodiments, a percentage is at least about 75%. In some embodiments, a percentage is at least about 80%. In some embodiments, a percentage is at least about 85%. In some embodiments, a percentage is at least about 90%. In some embodiments, a percentage is at least about 95%. In some embodiments, a percentage is about 100%. In some embodiments, a percentage is about or no more than about 5%. In some embodiments, a percentage is about or no more than about 10%. In some embodiments, a percentage is about or no more than about 15%. In some embodiments, a percentage is about or no more than about 20%. In some embodiments, a percentage is about or no more than about 25%. In some embodiments, a percentage is about or no more than about 30%. In some embodiments, a percentage is about or no more than about 35%. In some embodiments, a percentage is about or no more than about 40%. In some embodiments, a percentage is about or no more than about 45%. In some embodiments, a percentage is about or no more than about 50%. In some

embodiments, about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 1-5, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 internucleotidic linkages are independently *R*p chiral internucleotidic linkages. In some embodiments, the number is about or no more than about 1. In some embodiments, the number is about or no more than about 2. In some embodiments, the number is about or no more than about 3. In some embodiments, the number is about or no more than about 4. In some embodiments, the number is about or no more than about 5. In some embodiments, the number is about or no more than about 6. In some embodiments, the number is about or no more than about 7. In some embodiments, the number is about or no more than about 8. In some embodiments, the number is about or no more than about 9. In some embodiments, the number is about or no more than about 10.

[00519] In some embodiments, each phosphorothioate internucleotidic linkage in a third subdomain is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in a third subdomain is chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00520] In some embodiments, as illustrated in certain examples, a third subdomain comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in a third subdomain is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, it is about 1. In some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in a third subdomain are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of a third subdomain. In some embodiments, the last two or three or four internucleotidic linkages of a third subdomain comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In some embodiments, the last two or three or four internucleotidic linkages of a third subdomain comprise at least one internucleotidic linkage that is not n001. In some embodiments, the internucleotidic linkage linking the last two nucleosides

of a third subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a third subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a third subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a third subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of a third subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, the last two nucleosides of a third subdomain are the last two nucleosides of a second domain. In some embodiments, the last two nucleosides of a third subdomain are the last two nucleosides of an oligonucleotide. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a third subdomain is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a third subdomain is a *S*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a third subdomain is a *R*p non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a third subdomain is a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of a third subdomain is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage such as n001. In some embodiments, it is chirally controlled and is *R*p. In some embodiments, the last and/or the second last internucleotidic linkage of an oligonucleotide is a non-negatively charged internucleotidic linkage such as a phosphoryl guanidine internucleotidic linkage like n001. In some embodiments, it is chirally controlled and is *R*p.

[00521] In some embodiments, a third subdomain comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) natural phosphate linkages. In some embodiments, a third subdomain contains no natural phosphate linkages. In some embodiments, the internucleotidic linkage bonded to N_{-2} and N_{-3} is a natural phosphate linkage. In some embodiments, sugar of N_{-3} is a 2'-F modified sugar and sugar of N_{-2} is a 2'-OR modified sugar wherein R is not –H (e.g., a 2'-OMe modified sugar). In some embodiments, among all internucleotidic linkages bonded to two nucleosides of a third subdomain, one is a natural phosphate linkage (e.g., between N_{-2} and N_{-3} as described herein), one is a *R*p non-negatively charged internucleotidic linkage such as a phosphoryl guanidine internucleotidic linkage n001 (e.g., the last or the second last internucleotidic linkage of an oligonucleotide), and all the others are *S*p phosphorothioate internucleotidic linkages.

[00522] In some embodiments, a third subdomain comprises a 5'-end portion, e.g., one having a length of about 1-20, 1-15, 1-10, 1-8, 1-5, 1-3, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a 5'-end portion has a length of about 1-3 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases. In some embodiments, a length is 6 nucleobases. In some embodiments, a length is 7 nucleobases. In some

embodiments, a length is 8 nucleobases. In some embodiments, a length is 9 nucleobases. In some embodiments, a length is 10 nucleobases. In some embodiments, a 5'-end portion comprises the 5'-end nucleobase of a third subdomain. In some embodiments, a third subdomain comprises or consists of a 3'-end portion and a 5'-end portion. In some embodiments, a 5'-end portion comprises the 5'-end nucleobase of a third subdomain. In some embodiments, a 5'-end portion of a third subdomain is bonded to a second subdomain.

[00523] In some embodiments, a 5'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 5'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-20, 1-15, 1-10, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 5'-end portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00524] In some embodiments, one or more of the modified sugars independently comprises 2'-F or 2'-OR, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, one or more of the modified sugars are independently 2'-F or 2'-OMe. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 5'-end portion is independently a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl.

[00525] In some embodiments, compared to a 3'-end portion, 5' end portion contains a higher level (in numbers and/or percentage) of 2'-F modified sugars and/or sugars comprising two 2'-H (e.g., natural DNA sugars), and/or a lower level (in numbers and/or percentage) of other types of modified sugars, e.g., bicyclic sugars and/or sugars with 2'-OR modifications wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 3'-end portion, a 5'-end portion contains a higher level of 2'-F modified sugars and/or a lower level of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 3'-end portion, a 5'-end portion contains a higher level of 2'-F modified

sugars and/or a lower level of 2'-OMe modified sugars. In some embodiments, compared to a 3'-end portion, a 5'-end portion contains a higher level of natural DNA sugars and/or a lower level of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, compared to a 3'-end portion, a 5'-end portion contains a higher level of natural DNA sugars and/or a lower level of 2'-OMe modified sugars. In some embodiments, a 5'-end portion contains low levels (e.g., no more than 50%, 40%, 30%, 25%, 20%, or 10%, or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of modified sugars which are bicyclic sugars or sugars comprising 2'-OR wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl). In some embodiments, a 5'-end portion contains no modified sugars which are bicyclic sugars or sugars comprising 2'-OR wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl).

[00526] In some embodiments, one or more modified sugars independently comprise 2'-F. In some embodiments, no modified sugars comprises 2'-OMe or other 2'-OR modifications wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar of a 5'-end portion independently comprises two 2'-H or a 2'-F modification. In some embodiments, a 5'-end portion comprises 1, 2, 3, 4, or 5 2'-F modified sugars. In some embodiments, a 5'-end portion comprises 1-3 2'-F modified sugars. In some embodiments, a 5'-end portion comprises 1, 2, 3, 4, or 5 natural DNA sugars. In some embodiments, a 5'-end portion comprises 1-3 natural DNA sugars.

[00527] In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are *R*p. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 5'-end portion are *S*p. In some embodiments, each internucleotidic linkage of a 5'-end portion is *S*p. In some embodiments, a 5'-end portion contains a higher level (in number and/or percentage) of *R*p internucleotidic linkage and/or natural phosphate linkage compared to a 3'-end portion.

[00528] In some embodiments, a 5'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) mismatches as described herein. In some embodiments, a 5'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) wobbles as described herein. In some embodiments, a 5'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00529] In some embodiments, a third subdomain comprises a 3'-end portion, e.g., one having a length of

about 1-20, 1-15, 1-10, 1-8, 1-4, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleobases. In some embodiments, a 3'-end portion has a length of about 3-6 nucleobases. In some embodiments, a length is one nucleobase. In some embodiments, a length is 2 nucleobases. In some embodiments, a length is 3 nucleobases. In some embodiments, a length is 4 nucleobases. In some embodiments, a length is 5 nucleobases. In some embodiments, a length is 6 nucleobases. In some embodiments, a length is 7 nucleobases. In some embodiments, a length is 8 nucleobases. In some embodiments, a length is 9 nucleobases. In some embodiments, a length is 10 nucleobases. In some embodiments, a 3'-end portion comprises the 3'-end nucleobase of a third subdomain.

[00530] In some embodiments, a 3'-end portion comprises one or more sugars having two 2'-H (e.g., natural DNA sugars). In some embodiments, a 3'-end portion comprises one or more sugars having 2'-OH (e.g., natural RNA sugars). In some embodiments, one or more (e.g., about 1-20, 1-15, 1-10, 3-8, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) of sugars in a 3'-end portion are independently modified sugars. In some embodiments, about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in a 3'-end portion are independently modified sugars. In some embodiments, each sugar is independently a modified sugar. In some embodiments, modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

[00531] In some embodiments, one or more of the modified sugars independently comprises 2'-F or 2'-OR, wherein R is independently optionally substituted C_{1-6} aliphatic. In some embodiments, one or more of the modified sugars are independently 2'-F or 2'-OMe. In some embodiments, each modified sugar in a 3'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 3'-end portion is independently a bicyclic sugar (e.g., a LNA sugar) or a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar in a 3'-end portion is independently a sugar with a 2'-OR modification wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl.

[00532] In some embodiments, one or more sugars in a 3'-end portion independently comprise a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'–O–L^B–4' modification. In some embodiments, each sugar in a 3'-end portion independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'–O–L^B–4' modification. In some embodiments, L^B is optionally substituted $-CH_2-$. In some embodiments, L^B is $-CH_2-$. In some embodiments, each sugar in a 3'-end portion

independently comprises 2'-OMe.

[00533] In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a modified internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a chiral internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are independently a chirally controlled internucleotidic linkage. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are *R*p. In some embodiments, one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) internucleotidic linkages of a 3'-end portion are *S*p. In some embodiments, each internucleotidic linkage of a 3'-end portion is *S*p.

[00534] In some embodiments, a 3'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) mismatches as described herein. In some embodiments, a 3'-end portion comprises one or more (e.g., about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) wobbles as described herein. In some embodiments, a 3'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid. In some embodiments, a complementarity is 60% or more. In some embodiments, a complementarity is 70% or more. In some embodiments, a complementarity is 75% or more. In some embodiments, a complementarity is 80% or more. In some embodiments, a complementarity is 90% or more.

[00535] In some embodiments, a third subdomain recruits, promotes or contribute to recruitment of, a protein such as an ADAR protein, e.g., ADAR1, ADAR2, etc. In some embodiments, a third subdomain recruits, or promotes or contribute to interactions with, a protein such as an ADAR protein. In some embodiments, a third subdomain contacts with a RNA binding domain (RBD) of ADAR. In some embodiments, a third subdomain contacts with a catalytic domain of ADAR which has a deaminase activity. In some embodiments, a third subdomain contact with a domain that has a deaminase activity of ADAR1. In some embodiments, a third subdomain contact with a domain that has a deaminase activity of ADAR2. In some embodiments, various nucleobases, sugars and/or internucleotidic linkages of a third subdomain may interact with one or more residues of proteins, e.g., ADAR proteins.

[00536] As demonstrated herein, chiral control of linkage phosphorus of chiral internucleotidic linkages can be utilized in oligonucleotides to provide various properties and/or activities. In some embodiments, a *R*p internucleotidic linkage (e.g., a *R*p phosphorothioate internucleotidic linkage), a *S*p internucleotidic linkage (e.g., a *R*p phosphorothioate internucleotidic linkage), or a non-chirally controlled internucleotidic linkage (e.g., a non-chirally controlled phosphorothioate internucleotidic linkage) is at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine ("+" is counting from the nucleoside toward the 5'-end of an oligonucleotide with the internucleotidic linkage at the +1 position being the internucleotidic linkage between a nucleoside opposite to a target adenosine and its 5' side neighboring nucleoside (e.g., being the internucleotidic linkage bonded to the 5'-carbon of a nucleoside

opposite to a target adenosine, or being between N_1 and N_0 of 5'-$N_1N_0N_{-1}$-3', wherein as described herein N_0 is the nucleoside opposite to a target adenosine), and "-" is counting from the nucleoside toward the 3'-end of an oligonucleotide with the internucleotidic linkage at the -1 position being the internucleotidic linkage between a nucleoside opposite to a target adenosine and its 3' side neighboring nucleoside (e.g., being the internucleotidic linkage bonded to the 3'-carbon of a nucleoside opposite to a target adenosine, or being between N_{-1} and N_0 of 5'-$N_1N_0N_{-1}$-3', wherein as described herein N_0 is the nucleoside opposite to a target adenosine)). In some embodiments, a *R*p internucleotidic linkage (e.g., a *R*p phosphorothioate internucleotidic linkage) is at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a *R*p internucleotidic linkage (e.g., a *R*p phosphorothioate internucleotidic linkage) is at one or more of positions -2, -1, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a *S*p internucleotidic linkage (e.g., a *S*p phosphorothioate internucleotidic linkage) is at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a *S*p internucleotidic linkage (e.g., a *S*p phosphorothioate internucleotidic linkage) is at one or more of positions -2, -1, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a non-chirally controlled internucleotidic linkage (e.g., a non-chirally controlled phosphorothioate internucleotidic linkage) is at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a non-chirally controlled internucleotidic linkage (e.g., a non-chirally controlled phosphorothioate internucleotidic linkage) is at one or more of positions -2, -1, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine.

[00537] In some embodiments, Rp is at position +8. In some embodiments, Rp is at position +7. In some embodiments, Rp is at position −6. In some embodiments, Rp is at position +5. In some embodiments, Rp is at position +4. In some embodiments, Rp is at position +3. In some embodiments, Rp is at position +2. In some embodiments, Rp is at position +1. In some embodiments, Rp is at position -1. In some embodiments, Rp is at position -2. In some embodiments, Rp is at position -3. In some embodiments, Rp is at position -4. In some embodiments, Rp is at position -5. In some embodiments, Rp is at position -6. In some embodiments, Rp is at position -7. In some embodiments, Rp is at position -8. In some embodiments, Rp is the configuration of a chirally controlled phosphorothioate internucleotidic linkage. In some embodiments, Sp is at position +8. In some embodiments, Sp is at position +7. In some embodiments, Sp is at position −6. In some embodiments, Sp is at position +5. In some embodiments, Sp is at position +4. In some embodiments, Sp is at position +3. In some embodiments, Sp is at position +2. In some embodiments, Sp is at position +1. In some embodiments, Sp is at position -1. In some embodiments, Sp is at position -2. In some embodiments, Sp is at position -3. In some embodiments, Sp is at position -4. In some embodiments, Sp is at position -5. In some embodiments, Sp is at position -6. In some embodiments, Sp is at position -7. In some embodiments, Sp is at position -8. In some embodiments, Sp is the configuration of a chirally controlled phosphorothioate internucleotidic linkage. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +8. In some

embodiments, a non-chirally controlled internucleotidic linkage is at position +7. In some embodiments, a non-chirally controlled internucleotidic linkage is at position −6. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +5. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +4. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +3. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +2. In some embodiments, a non-chirally controlled internucleotidic linkage is at position +1. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -1. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -2. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -3. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -4. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -5. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -6. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -7. In some embodiments, a non-chirally controlled internucleotidic linkage is at position -8. In some embodiments, a non-chirally controlled internucleotidic linkage is a non-chirally controlled phosphorothioate internucleotidic linkage.

[00538] In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *R*p internucleotidic linkages (e.g., *R*p phosphorothioate internucleotidic linkages). In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *S*p internucleotidic linkages (e.g., *S*p phosphorothioate internucleotidic linkages). In some embodiments, a first domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled internucleotidic linkages (e.g., non-chirally controlled phosphorothioate internucleotidic linkages). In some embodiments, such internucleotidic linkages are consecutive. In some embodiments, at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all of internucleotidic linkages in a first domain are chirally controlled and are *S*p. In some embodiments, at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all of phosphorothioate internucleotidic linkages in a first domain are chirally controlled and are *S*p. In some embodiments, a second domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *R*p internucleotidic linkages (e.g., *R*p phosphorothioate internucleotidic linkages). In some embodiments, a second domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *S*p internucleotidic linkages (e.g., *S*p phosphorothioate internucleotidic linkages). In some embodiments, a second domain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled internucleotidic linkages (e.g., non-chirally controlled phosphorothioate internucleotidic linkages). In some embodiments, such internucleotidic linkages are consecutive. In some embodiments, at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all of internucleotidic linkages in a second domain are chirally controlled and are *S*p. In some embodiments, at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all of phosphorothioate internucleotidic linkages in a second domain are chirally controlled and are *S*p. In some embodiments, a first subdomain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *R*p internucleotidic linkages (e.g., *R*p phosphorothioate internucleotidic linkages). In some embodiments, a first subdomain comprises one or more

(e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) *S*p internucleotidic linkages (e.g., *S*p phosphorothioate internucleotidic linkages). In some embodiments, a first subdomain comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled internucleotidic linkages (e.g., non-chirally controlled phosphorothioate internucleotidic linkages). In some embodiments, such internucleotidic linkages are consecutive. In some embodiments, such internucleotidic linkages are at 3'-end portion of a first subdomain.

[00539] In some embodiments, one or more natural phosphate linkages are utilized in provided oligonucleotides and compositions thereof. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise one or more (e.g., about, or at least about, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, or more) natural phosphate linkages. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise two or more (e.g., about, or at least about, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, or more) consecutive natural phosphate linkages. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise no more than about, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 natural phosphate linkages. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise no more than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 consecutive natural phosphate linkages. In some embodiments, about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all internucleotidic linkages in provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) are natural phosphate linkages. In some embodiments, about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all internucleotidic linkages in provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) are not natural phosphate linkages. In some embodiments, about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all internucleotidic linkages in provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) are not consecutive natural phosphate linkages.

[00540] In some embodiments, provided oligonucleotides or portions thereof comprises one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, provided oligonucleotides or portions thereof comprises one or more natural phosphate linkages and one or more chirally controlled modified internucleotidic linkages. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.)

comprise no more than about, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 natural phosphate linkages each of which independently bonds to two sugars comprising no 2'-OR modification, wherein R is as described herein but not −H. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise no more than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 consecutive natural phosphate linkages each of which independently bonds to two sugars comprising no 2'-OR modification, wherein R is as described herein but not −H. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise no more than about, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 natural phosphate linkages each of which independently bonds to two 2'-F modified sugars. In some embodiments, provided oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) comprise no more than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 consecutive natural phosphate linkages each of which independently bonds to two 2'-F modified sugars. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, e.g., no more than 2, no more than 3, no more than 4, no more than 5, etc., internucleotidic linkages that bond to two sugars comprising no 2'-OR modification wherein R is as described herein but not −H are natural phosphate linkages. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, e.g., no more than 2, no more than 3, no more than 4, no more than 5, etc., internucleotidic linkages that bond to two 2'-F modified sugars are natural phosphate linkages. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) no more than about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, e.g., no more than 10%, no more than 15%, no more than 20%, no more than 25%, no more than about 30%, no more than about 40%, no more than 50% etc., of internucleotidic linkages that bond to two sugars comprising no 2'-OR modification wherein R is as described herein but not −H are natural phosphate linkages. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) no more than about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, e.g., no more than 10%, no more than 15%, no more than 20%, no more than 25%, no more than about 30%, no more than about 40%, no more than 50% etc., of internucleotidic linkages that bond to two 2'-F modified sugars are natural phosphate linkages. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains,

second subdomains, third subdomains, etc.) no more than about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, e.g., no more than 2, no more than 3, no more than 4, no more than 5, etc., consecutive internucleotidic linkages that bond to two sugars comprising no 2'-OR modification wherein R is as described herein but not −H are natural phosphate linkages. In some embodiments, in oligonucleotides or portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, third subdomains, etc.) no more than about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50, e.g., no more than 2, no more than 3, no more than 4, no more than 5, etc., consecutive internucleotidic linkages that bond to two 2'-F modified sugars are natural phosphate linkages.

[00541] In some embodiments, a natural phosphate linkage is at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine. In some embodiments, a natural phosphate linkage is at one or more of positions -1 and +1. In some embodiments, a natural phosphate linkage is at positions -1 and +1. In some embodiments, a natural phosphate linkage is at position -1. In some embodiments, a natural phosphate linkage is at position +1. In some embodiments, a natural phosphate linkage is at position +8. In some embodiments, a natural phosphate linkage is at position +7. In some embodiments, a natural phosphate linkage is at position −6. In some embodiments, a natural phosphate linkage is at position +5. In some embodiments, a natural phosphate linkage is at position +4. In some embodiments, a natural phosphate linkage is at position +3. In some embodiments, a natural phosphate linkage is at position +2. In some embodiments, a natural phosphate linkage is at position -2. In some embodiments, a natural phosphate linkage is at position -3. In some embodiments, a natural phosphate linkage is at position -4. In some embodiments, a natural phosphate linkage is at position -5. In some embodiments, a natural phosphate linkage is at position -6. In some embodiments, a natural phosphate linkage is at position -7. In some embodiments, a natural phosphate linkage is at position -8. In some embodiments, a natural phosphate linkage is at position -1, and a modified internucleotidic linkage is at position +1. In some embodiments, a natural phosphate linkage is at position +1, and a modified internucleotidic linkage is at position -1. In some embodiments, a modified internucleotidic linkage is chirally controlled. In some embodiments, a modified internucleotidic linkage is chirally controlled and is Sp. In some embodiments, a modified internucleotidic linkage is a chirally controlled Sp phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is chirally controlled and is Rp. In some embodiments, a modified internucleotidic linkage is a chirally controlled Rp phosphorothioate internucleotidic linkage. In some embodiments, a second domain comprises no more than 2 natural phosphate linkages. In some embodiments, a second domain comprises no more than 1 natural phosphate linkages. In some embodiments, a single natural phosphate linkage can be utilized at various positions of an oligonucleotide or a portion thereof (e.g., a first domain, a second domain, a first subdomain, a second subdomain, a third subdomain, etc.).

[00542] In some embodiments, particular types of sugars are utilized at particular positions of oligonucleotides or portions thereof. For example, in some embodiments, a first domain comprises a number

of 2’-F modified sugars (and optionally a number of 2’-OR modified sugars wherein R is not–H, in some embodiments at lower levels than 2’-F modified sugars), a first subdomain comprises a number of 2’-OR modified sugars wherein R is not–H (e.g., 2’-OMe modified sugars; and optionally a number of 2’-F sugars, in some embodiments at lower levels than 2’-OR modified sugars wherein R is not –H), a second domain comprises one or more natural DNA sugars (no substitution at 2’ position) and/or one or more 2’-F modified sugars, and/or a third subdomain comprises a number of 2’-OR modified sugars wherein R is not–H (e.g., 2’-OMe modified sugars; and optionally a number of 2’-F sugars, in some embodiments at lower levels than 2’-OR modified sugars wherein R is not –H). In some embodiments, particular type of sugars are independently at one or more of positions -8, -7, -6, -5, -4, -3, -2, -1, 0, +1, +2, +3, +4, +5, +6, +7, and +8 of a nucleoside opposite to a target adenosine (“+” is counting from the nucleoside toward the 5’-end of an oligonucleotide, “-” is counting from the nucleoside toward the 3’-end of an oligonucleotide, with position 0 being the position of the nucleoside opposite to a target adenosine, e.g.: 5’- … $N_{+2}N_{+1}N_0N_{-1}N_{-2}$….3’). In some embodiments, particular types of sugars are independently at one or more of positions -5, -4, -3, -2, -1, 0, +1, +2, +3, +4, and +5. In some embodiments, particular types of sugars are independently at one or more of positions -3, -2, -1, 0, +1, +2, and +3. In some embodiments, particular types of sugars are independently at one or more of positions -2, -1, 0, +1, and +2. In some embodiments, particular types of sugars are independently at one or more of positions -1, 0, and +1. In some embodiments, a particular type of sugar is at position +8. In some embodiments, a particular type of sugar is at position +7. In some embodiments, a particular type of sugar is at position +6. In some embodiments, a particular type of sugar is at position +5. In some embodiments, a particular type of sugar is at position +4. In some embodiments, a particular type of sugar is at position +3. In some embodiments, a particular type of sugar is at position +2. In some embodiments, a particular type of sugar is at position +1. In some embodiments, a particular type of sugar is at position 0. In some embodiments, a particular type of sugar is at position -8. In some embodiments, a particular type of sugar is at position -7. In some embodiments, a particular type of sugar is at position -6. In some embodiments, a particular type of sugar is at position -5. In some embodiments, a particular type of sugar is at position -4. In some embodiments, a particular type of sugar is at position -3. In some embodiments, a particular type of sugar is at position -2. In some embodiments, a particular type of sugar is at position -1. In some embodiments, a particular type of sugar is independently a sugar selected from a natural DNA sugar (two 2’-H at 2’-carbon), a 2’-OMe modified sugar, and a 2’-F modified sugar. In some embodiments, a particular type of sugar is independently a sugar selected from a natural DNA sugar (two 2’-H at 2’-carbon) and a 2’-OMe modified sugar. In some embodiments, a particular type of sugar is independently a sugar selected from a natural DNA sugar (two 2’-H at 2’-carbon) and a 2’-F modified sugar, e.g., for sugars at position 0, -1, and/or +1. In some embodiments, a particularly type of sugar is a natural DNA sugar (two 2’-H at 2’-carbon), e.g., at position -1, 0 or +1. In some embodiments, a particular type of sugar is 2’-F modified sugar, e.g., at position -8, -7, -6, -5, -4, -3, -2, -1, 0, +1, +2, +3, +4, +5, +6, +7, and/or +8. In some embodiments, a particular type of sugar is 2’-F modified sugar, e.g., at position -8, -7, -6, -5, -4, -3, -2, +2, +3, +4, +5, +6, +7, and/or +8. In some embodiments, a 2’-

F modified sugar is at position -2. In some embodiments, a 2'-F modified sugar is at position -3. In some embodiments, a 2'-F modified sugar is at position -4. In some embodiments, a 2'-F modified sugar is at position +2. In some embodiments, a 2'-F modified sugar is at position +3. In some embodiments, a 2'-F modified sugar is at position +4. In some embodiments, a 2'-F modified sugar is at position +5. In some embodiments, a 2'-F modified sugar is at position +6. In some embodiments, a 2'-F modified sugar is at position +7. In some embodiments, a 2'-F modified sugar is at position +8. In some embodiments, a particular type of sugar is 2'-OMe modified sugar, e.g., at position -8, -7, -6, -5, -4, -3, -2, -1, 0, +1, +2, +3, +4, +5, +6, +7, and/or +8. In some embodiments, a particular type of sugar is 2'-OMe modified sugar, e.g., at position -8, -7, -6, -5, -4, -3, -2, +2, +3, +4, +5, +6, +7, and/or +8. In some embodiments, a 2'-OMe modified sugar is at position -2. In some embodiments, a 2'-OMe modified sugar is at position -3. In some embodiments, a 2'-OMe modified sugar is at position -4. In some embodiments, a 2'-OMe modified sugar is at position +2. In some embodiments, a 2'-OMe modified sugar is at position +3. In some embodiments, a 2'-OMe modified sugar is at position +4. In some embodiments, a 2'-OMe modified sugar is at position +5. In some embodiments, a 2'-OMe modified sugar is at position +6. In some embodiments, a 2'-OMe modified sugar is at position +7. In some embodiments, a 2'-OMe modified sugar is at position +8. In some embodiments, a sugar at position 0 is not a 2'-MOE modified sugar. In some embodiments, a sugar at position 0 is a natural DNA sugar (two 2'-H at 2'-carbon). In some embodiments, a sugar at position 0 is not a 2'-MOE modified sugar. In some embodiments, a sugar at position -1 is not a 2'-MOE modified sugar. In some embodiments, a sugar at position -2 is not a 2'-MOE modified sugar. In some embodiments, a sugar at position -3 is not a 2'-MOE modified sugar. In some embodiments, a first domain comprises one or more 2'-F modified sugars, and optionally 2'-OR modified sugars (in some embodiments at lower levels than 2'-F modified sugars) wherein R is as described herein and is not –H. In some embodiments, a first domain comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-OR modified sugars (in some embodiments at lower levels that 2'-F modified sugars) wherein R is as described herein and is not –H. In some embodiments, a first domain comprise 1, 2, 3, or 4, or 1 and no more than 1, 2 and no more than 2, 3 and no more than 3, or 4 and no more than 4 2'-OR modified sugars wherein R is C_{1-6} aliphatic. In some embodiments, the first, second, third and/or fourth sugars of a first domain are independently 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, sugars comprising 2'-OR are consecutive. In some embodiments, a first domain comprises 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive sugars at its 5'-end, wherein each sugar independently comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, 2'-OR is 2'-OMe. In some embodiments, 2'-OR is 2'-MOE. In some embodiments, a second domain comprises one or more 2'-OR modified sugars (in some embodiments at lower levels) wherein R is as described herein and is not –H, and optionally 2'-F modified sugars (in some embodiments at lower levels). In some embodiments, a first subdomain comprises one or more 2'-OR modified sugars (in some embodiments at lower levels) wherein R is as described herein and is not –H, and optionally 2'-F modified sugars (in some embodiments at lower levels). In some embodiments, a third subdomain comprises one or more 2'-OR modified sugars (in some

embodiments at lower levels) wherein R is as described herein and is not −H, and optionally 2'-F modified sugars (in some embodiments, at lower levels; in some embodiments, at higher levels). In some embodiments, a third subdomain comprises about, or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 2'-F modified sugars. In some embodiments, a third subdomain comprises about, or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive 2'-F modified sugars. In some embodiments, about or at least about, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of sugars in a third subdomain independently comprise 2'-F modification. In some embodiments, the first 2'-F modified sugar in the third subdomain (from 5' to 3') is not the first sugar in the third subdomain. In some embodiments, the first 2'-F modified sugar in the third subdomain is at position -3 relative to the nucleoside opposition to a target adenosine. In some embodiments, each sugar in a third subdomain is independently a modified sugar. In some embodiments, each sugar in a third subdomain is independently a modified sugar, wherein the modification is selected from 2'-F and 2'-OR, wherein R is C_{1-6} aliphatic. In some embodiments, a modification in selected from 2'-F and 2'-OMe. In some embodiments, each modified sugar in a third subdomain is independently 2'-F modified sugar. In some embodiments, each modified sugar in a third subdomain is independently 2'-OMe modified sugar. In some embodiments, one or more modified sugars in a third subdomain are independently 2'-OMe modified sugar, and one or more modified sugars in a third subdomain are independently 2'-F modified sugar. In some embodiments, each modified sugar in a third subdomain is independently a 2'-F modified sugar except the first sugar of a third subdomain, which in some embodiments is a 2'-OMe modified sugar. In some embodiments, a third subdomain comprises one or more 2'-OR modified sugars (in some embodiments at lower levels) wherein R is as described herein and is not −H, and optionally 2'-F modified sugars (in some embodiments at lower levels). In some embodiments, 2'-OR is 2'-OMe. In some embodiments, 2'-OR is 2'-MOE.

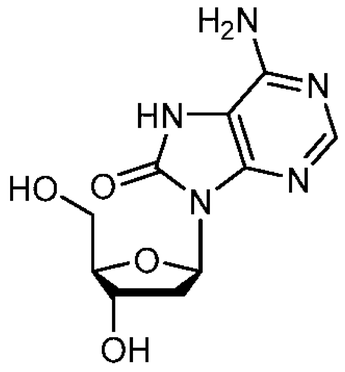
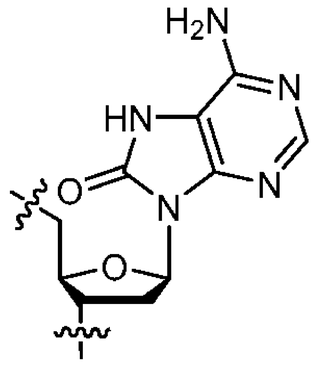
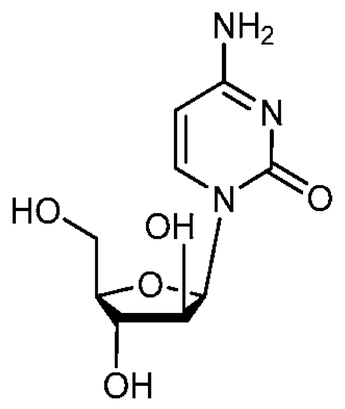
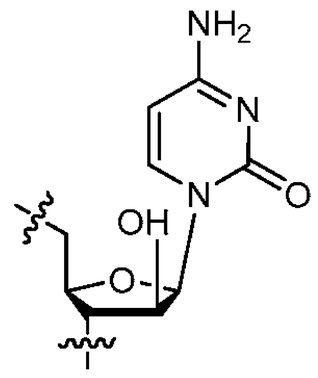
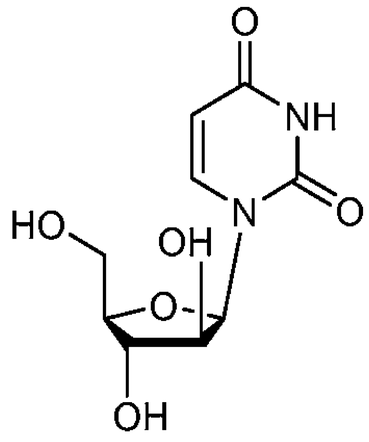
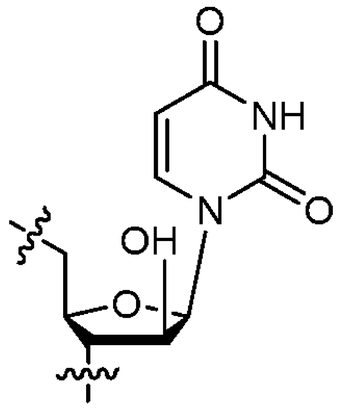
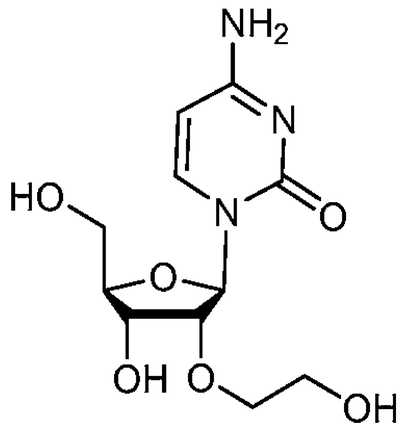
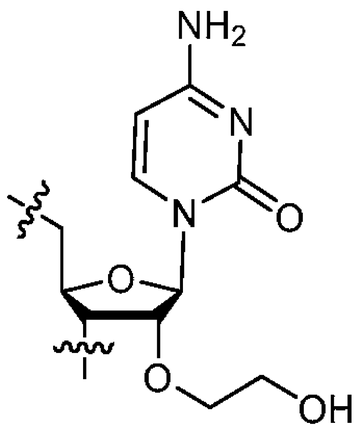
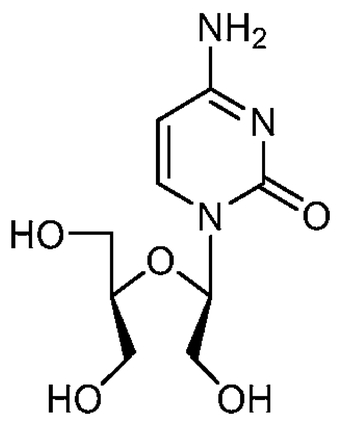
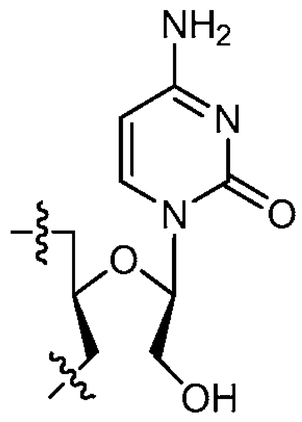
Editing Region

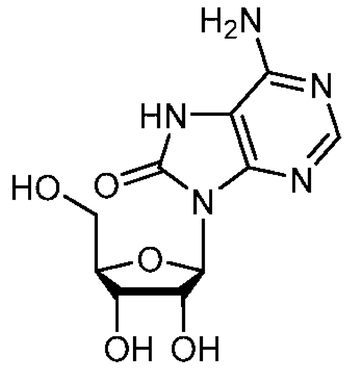
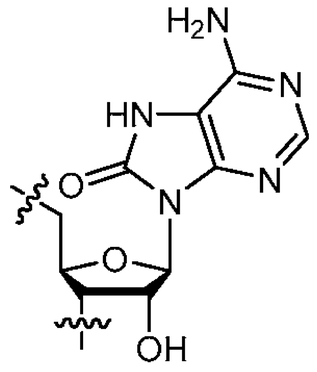
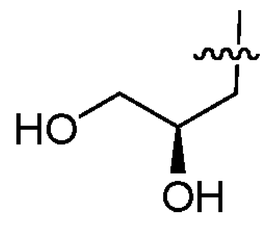
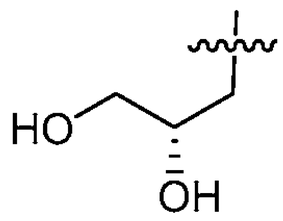
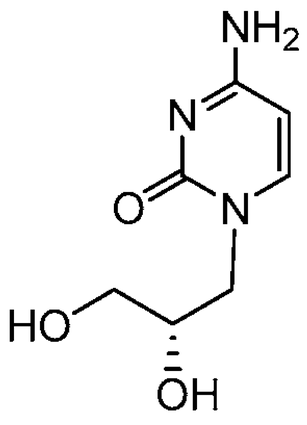
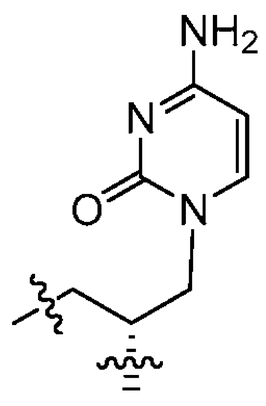
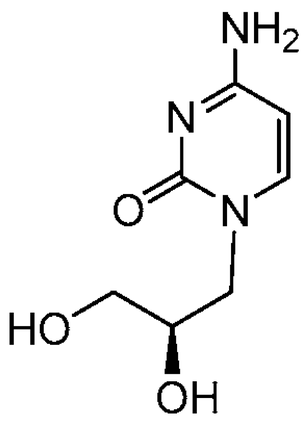
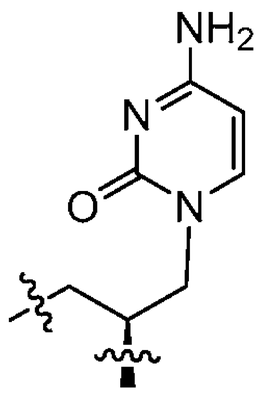
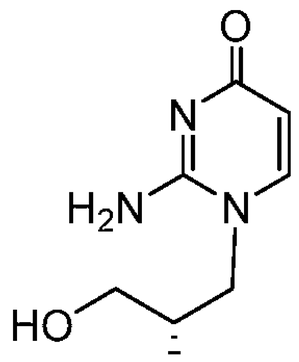
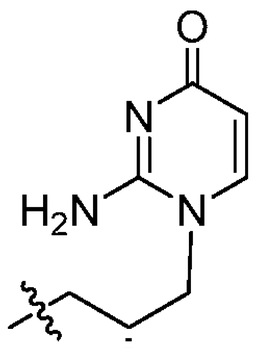
[00543] In some embodiments, the present disclosure provides oligonucleotides comprising editing regions, e.g., regions comprising or consisting of 5'-$N_1N_0N_{-1}$−3' as described herein. In some embodiments, an editing region is or comprises a nucleoside opposite to a target adenosine (typically, when base sequences of oligonucleotides are aligned with target sequences for maximal complementarity, and/or oligonucleotides hybridize with target nucleic acids) and its neighboring nucleosides. In some embodiments, an editing region is or comprises three nucleobases, wherein the nucleobase in the middle is a nucleoside opposite to a target adenosine. In some embodiments, a nucleoside opposite to a target adenosine is N_0 as described herein.

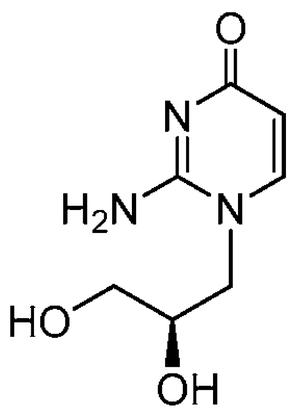
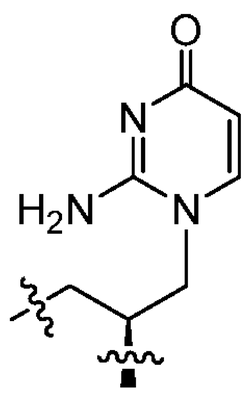
[00544] In some embodiments, the nucleobase of a nucleoside opposite to a target adenosine (may be referred to as BA_0) is C. In some embodiments, BA_0 is a modified nucleobase as described herein. In some embodiments, a nucleobase, e.g., BA_0, is or comprises Ring BA which has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected. In some embodiments, a nucleobase is optionally substituted or protected, or optionally substituted or protected

tautomer of C, T, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, and zdnp. In some embodiments, a nucleobase is optionally substituted or protected, or optionally substituted or protected tautomer of zdnp, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b001A, b002A, b003A, b001C, b002C, b003C, b002I, b003I, or b001G. In some embodiments, the nucleobase of N_0 is optionally substituted or protected, or optionally substituted or protected tautomer of C, zdnp, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b001A, b002A, b003A, b001C, b002C, b003C, b002I, b003I, or b001G, and the sugar of N_0 is a natural DNA sugar. In some embodiments, the nucleobase of N_0 is optionally substituted or protected, or optionally substituted or protected tautomer of C, zdnp, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b001A, b002A, b003A, b001C, b002C, b003C, b002I, b003I, or b001G, and the sugar of N_0 is a natural RNA sugar. In some embodiments, BA_0 is C. In some embodiments, BA_0 is T. In some embodiments, BA_0 is hypoxanthine. In some embodiments, BA_0 is U. In some embodiments, BA_0 is b001U. In some embodiments, BA_0 is b002U. In some embodiments, BA_0 is b003U. In some embodiments, BA_0 is b004U. In some embodiments, BA_0 is b005U. In some embodiments, BA_0 is b006U. In some embodiments, BA_0 is b007U. In some embodiments, BA_0 is b008U. In some embodiments, BA_0 is b009U. In some embodiments, BA_0 is b011U. In some embodiments, BA_0 is b012U. In some embodiments, BA_0 is b013U. In some embodiments, BA_0 is b001A. In some embodiments, BA_0 is b002A. In some embodiments, BA_0 is b003A. In some embodiments, BA_0 is b001C. In some embodiments, BA_0 is b002C. In some embodiments, BA_0 is b003C. In some embodiments, BA_0 is b004C. In some embodiments, BA_0 is b005C. In some embodiments, BA_0 is b006C. In some embodiments, BA_0 is b007C. In some embodiments, BA_0 is b008C. In some embodiments, BA_0 is b009C. In some embodiments, BA_0 is b002I. In some embodiments, BA_0 is b003I. In some embodiments, BA_0 is b004I. In some embodiments, BA_0 is b014I. In some embodiments, BA_0 is b001G. In some embodiments, BA_0 is b002G. In some embodiments, sugar of N_0 is a natural DNA sugar, or a substituted natural DNA sugar one of whose 2'-H is substituted with −OH or −F and the other 2'-H is not substituted. In some embodiments, sugar of N_0 is a natural DNA sugar. In some embodiments, sugar of N_0 is a natural RNA sugar. In some embodiments, sugar of N_0 is an acyclic sugar. In some embodiments, sugar of N_0 is sm01. In some embodiments, sugar of N_0 is sm04. In some embodiments, sugar of N_0 is sm11. In some embodiments, sugar of N_0 is sm12. In some embodiments, sugar of N_0 is rsm13. In some embodiments, sugar of N_0 is rsm14. In some embodiments, sugar of N_0 is sm15. In some embodiments, sugar of N_0 is sm16. In some embodiments, sugar of N_0 is sm17. In some embodiments, sugar of N_0 is sm18. Among other things, the present disclosure confirmed that various modified nucleobases and/or various sugars may be utilized at N_0 in oligonucleotides to provide adenosine-editing activities. In some embodiments, it was observed that b001A as BA_0 can provide improved adenosine editing efficiency compared to a reference nucleobase (e.g., under comparable conditions including in otherwise identical oligonucleotides, assessed in identical or comparable assays, etc.). In some embodiments, it was observed that b008U as BA_0

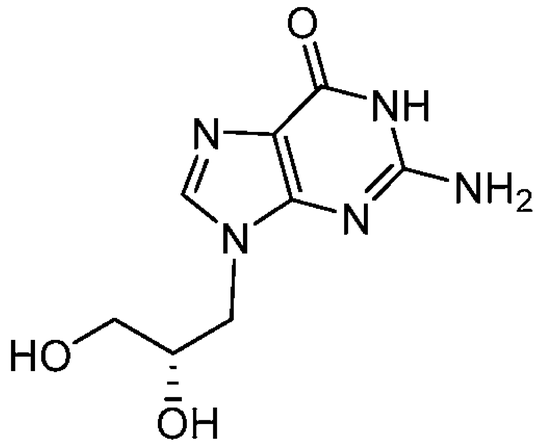
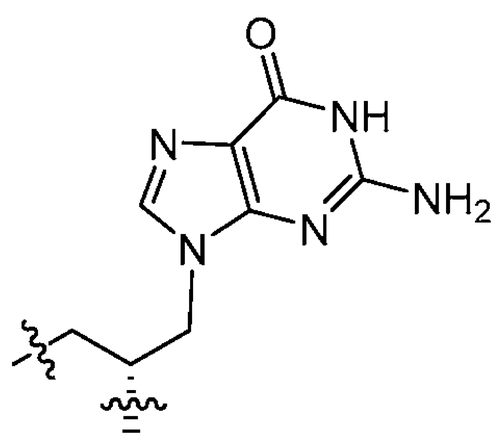
can provide improved adenosine editing efficiency. In some embodiments, a reference nucleobase is U. In some embodiments, a reference nucleobase is T. In some embodiments, a reference nucleobase is C.

[00545] In some embodiments, a nucleoside opposite to a target adenosine, e.g., N_0, is dC. In some embodiments, it is rC. In some embodiments, it is fC. In some embodiments, it is dT. In some embodiments, it is rT. In some embodiments, it is fT. In some embodiments, it is dU. In some embodiments, it is rU. In some embodiments, it is fU. In some embodiments, it is b001A (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Csm15 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Usm15 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is rCsm13 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Csm04 (which when utilized for a nucleoside refers to  or 

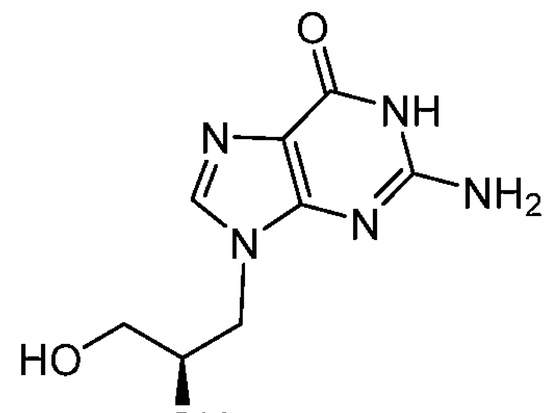
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b001rA (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, a sugar is a (R)-GNA sugar  . In some embodiments, a sugar is a (S)-GNA sugar  . In some embodiments, it is S-GNA C, also referred herein as Csm11 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is R-GNA C, also referred herein as Csm12 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is S-GNA isoC, also referred herein as b009Csm11 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is R-GNA isoC, also referred herein as b009Csm12 (which

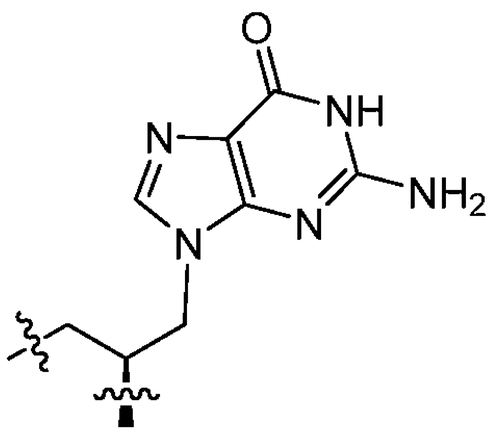
when utilized for a nucleoside refers to or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is S-GNA G, also referred herein as Gsm11 (which when

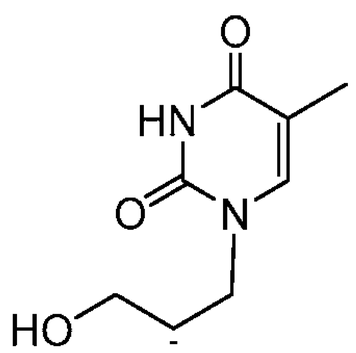
utilized for a nucleoside refers to or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is R-GNA G, also referred herein



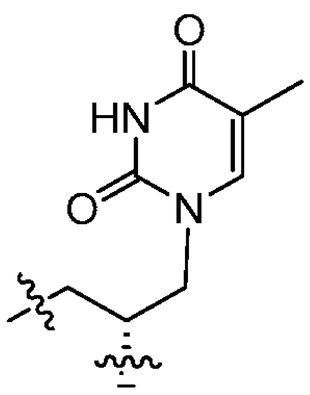
as Gsm12 (which when utilized for a nucleoside refers to OH or



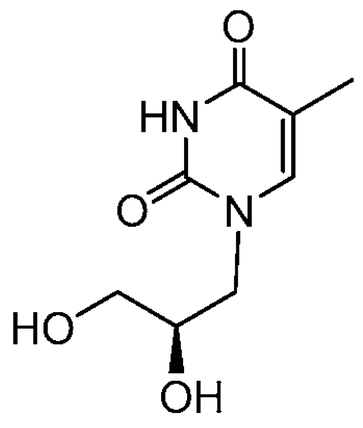
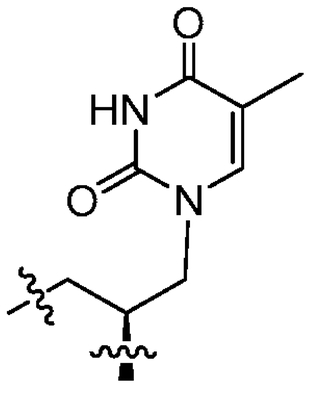
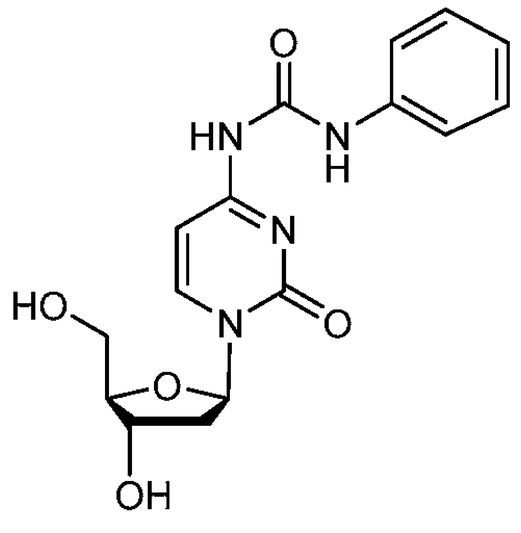
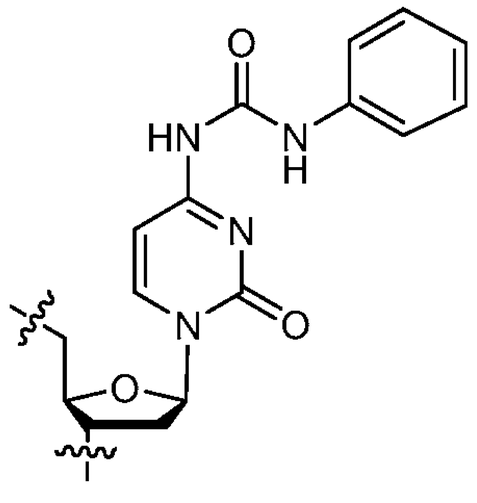
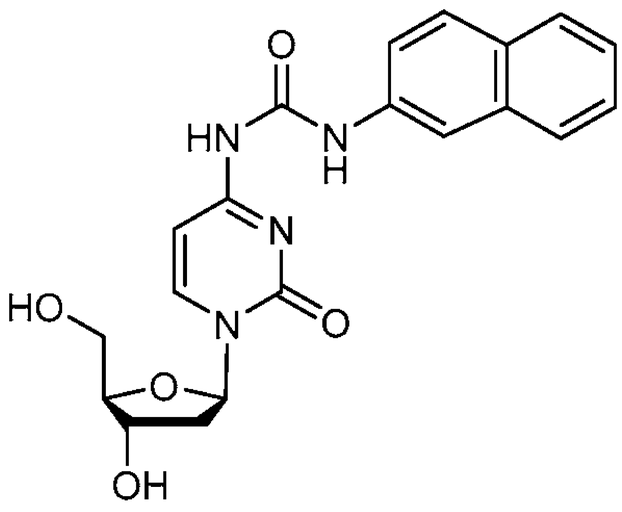
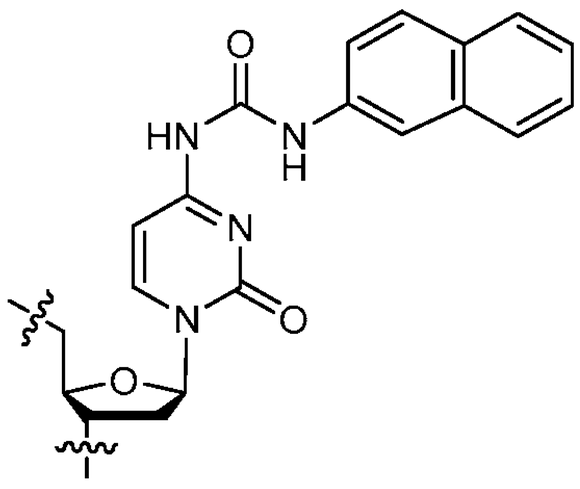
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is

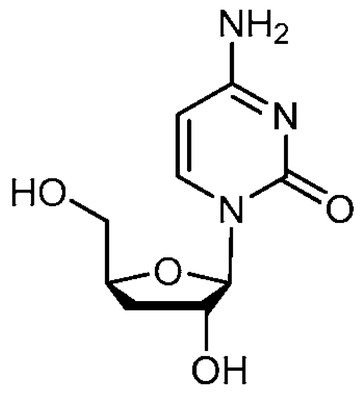


S-GNA T, also referred herein as Tsm11 (which when utilized for a nucleoside refers to OH or

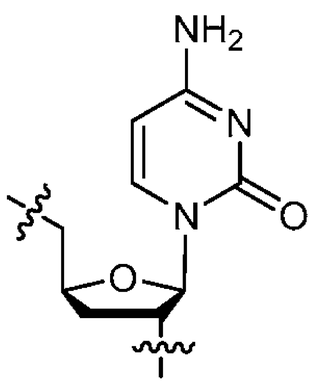


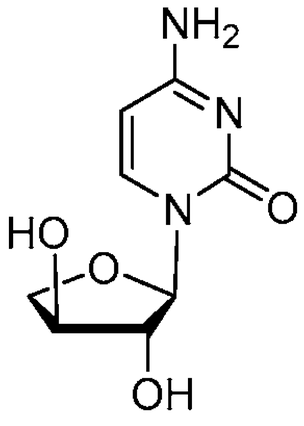
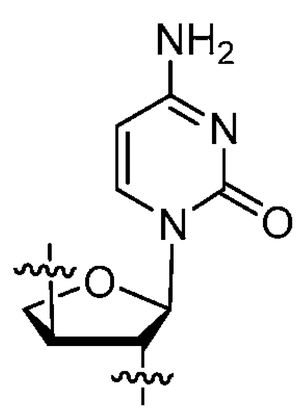
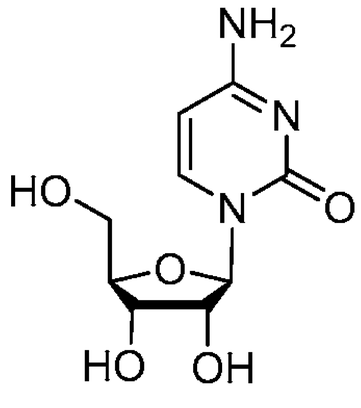
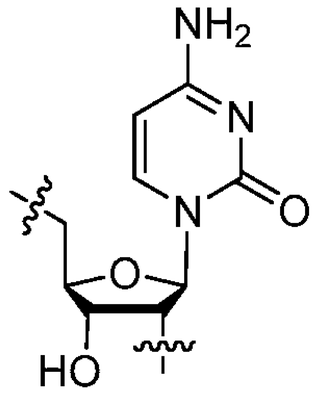
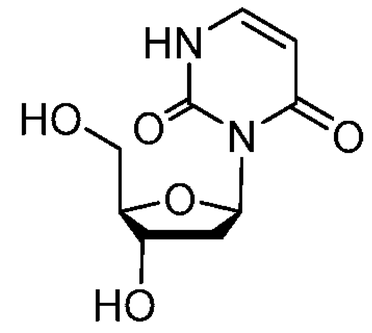
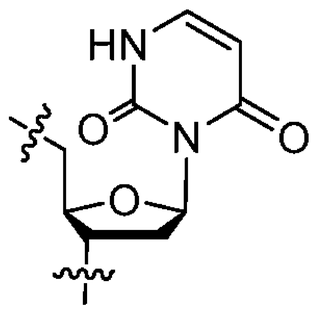
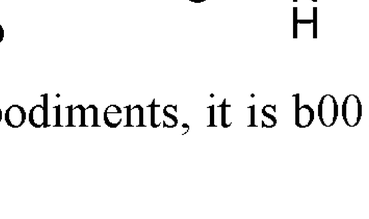
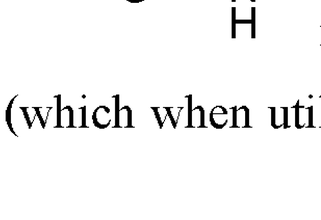
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is R-GNA

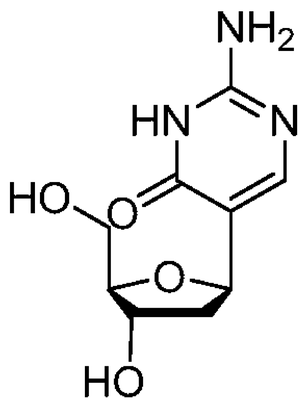
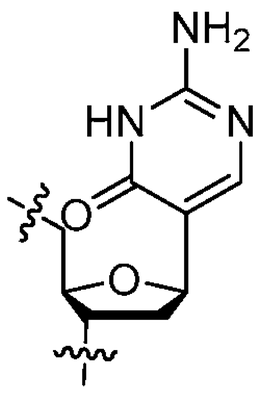
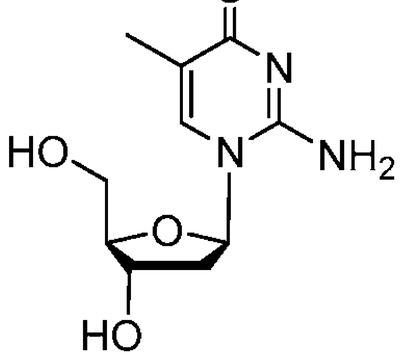
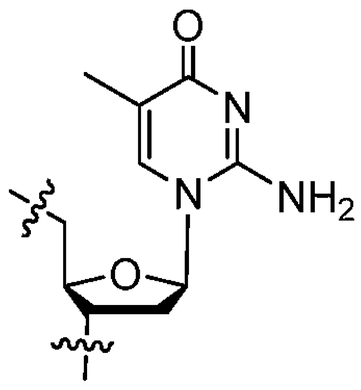
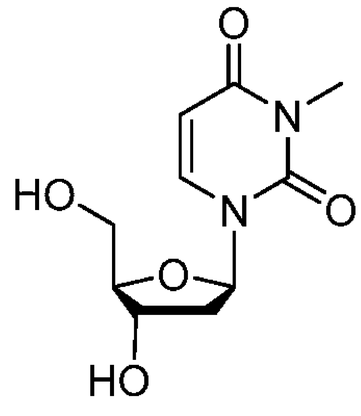
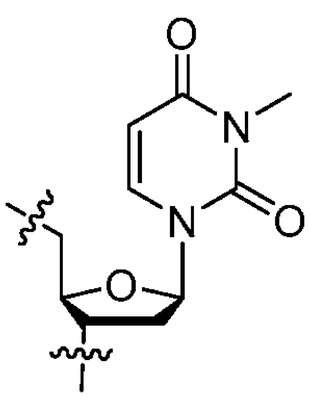
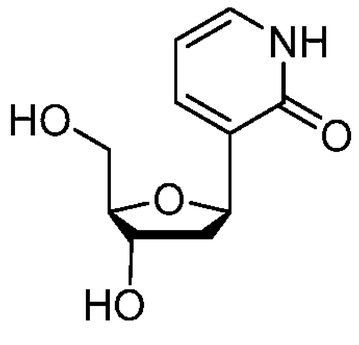
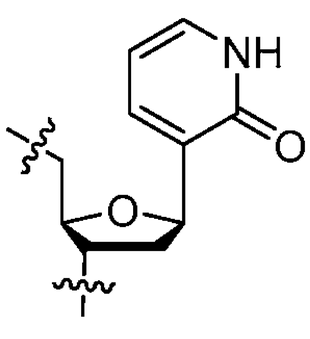
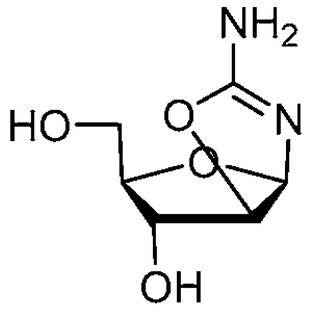
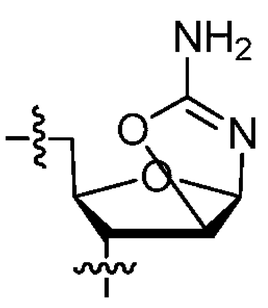
T, also referred herein as Tsm12 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b004C (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b007C (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise).

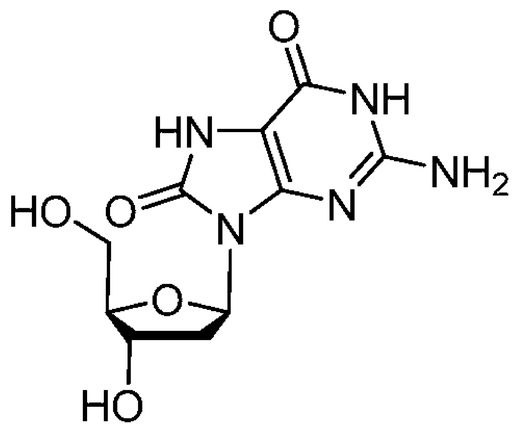
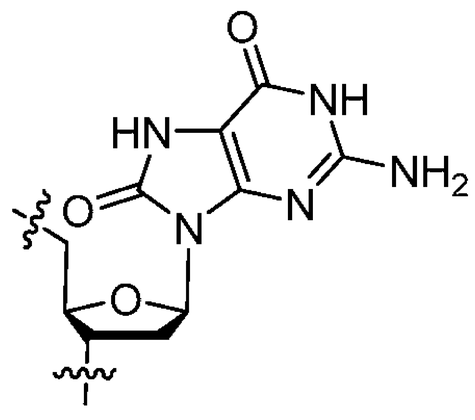


In some embodiments, it is Csm16 (which when utilized for a nucleoside refers to  or

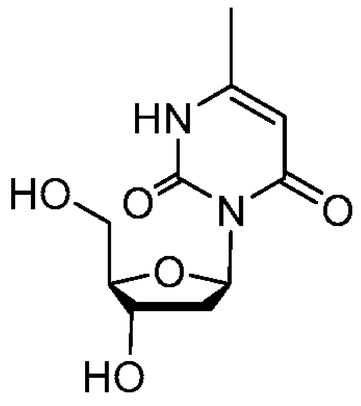
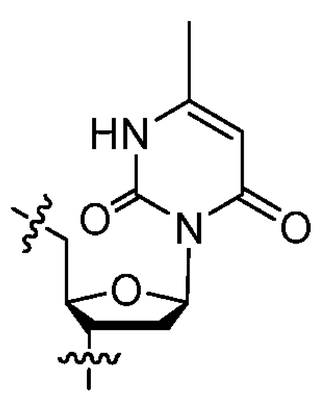


in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Csm17 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is rCsm14 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b008U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b010U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b001C (which when utilized for a nucleoside

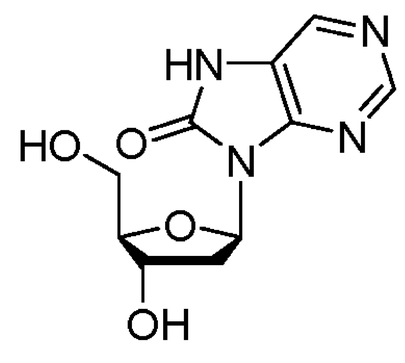
refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b008C (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b011U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b012U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is abasic. In some embodiments, it is L010. In some embodiments, it is L034 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b002G (which when utilized for a nucleoside refers to

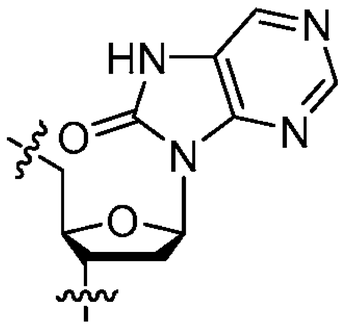
or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b013U (which when utilized for a nucleoside refers to

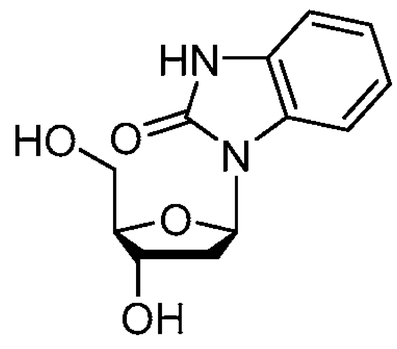
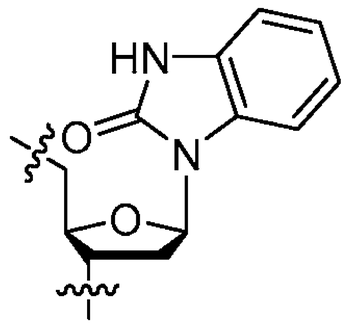
or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b002A (which when utilized for a nucleoside refers to



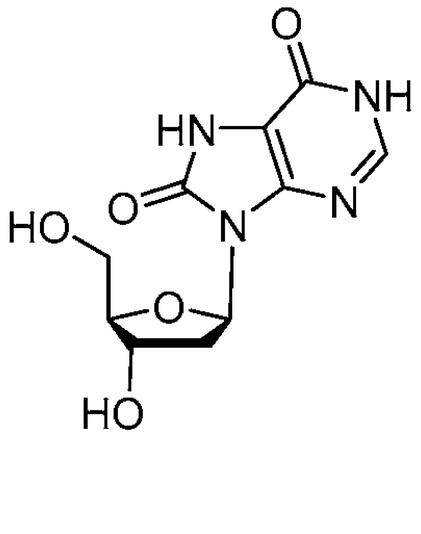
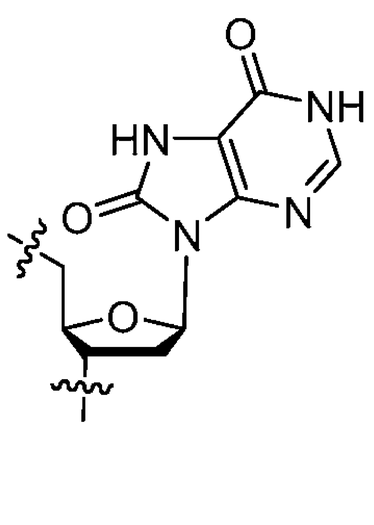
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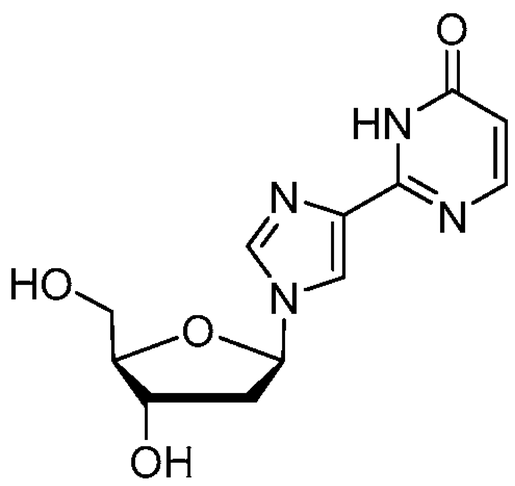
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b003A (which when utilized for a nucleoside refers to

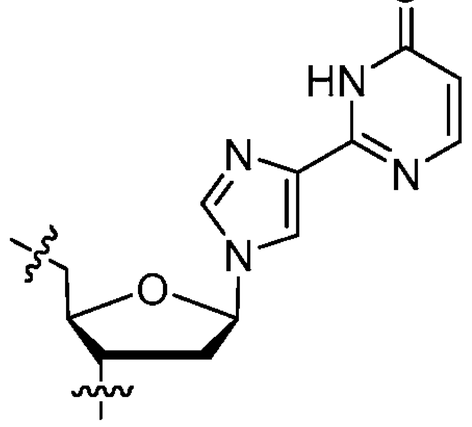
or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b004I (which when utilized for a nucleoside refers to

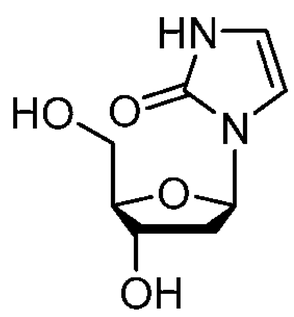
or in an oligonucleotide chain unless specified otherwise).



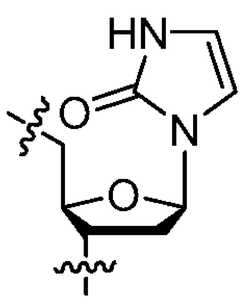
In some embodiments, it is b014I (which when utilized for a nucleoside refers to



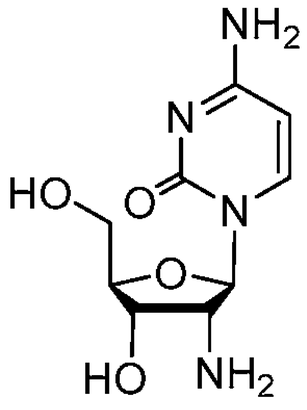
or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b009U (which when utilized for a nucleoside refers to



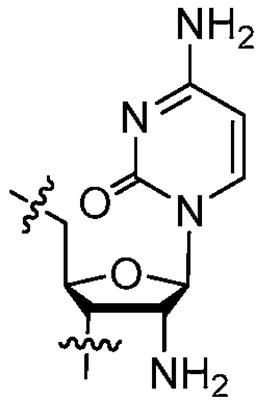
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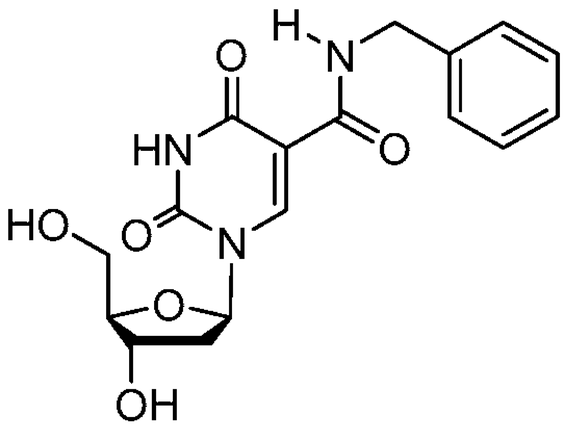
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is aC (which when utilized for a nucleoside refers to



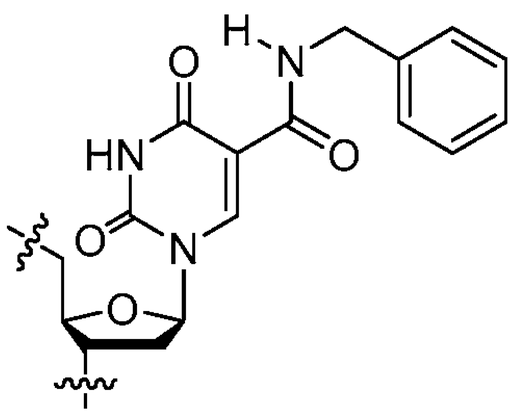
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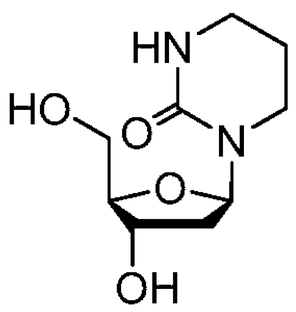
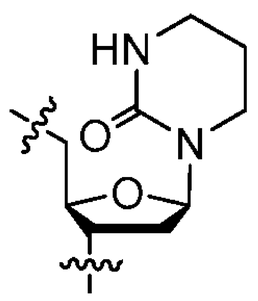
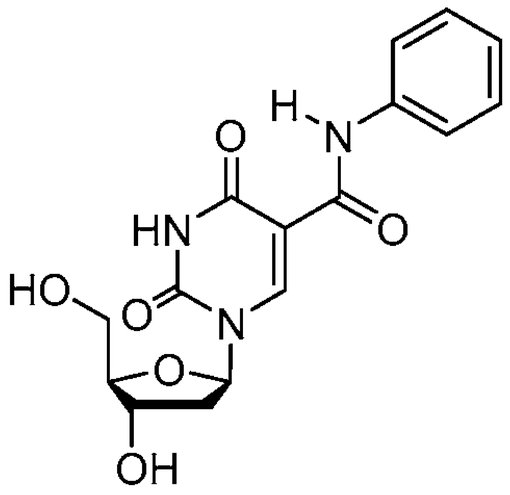
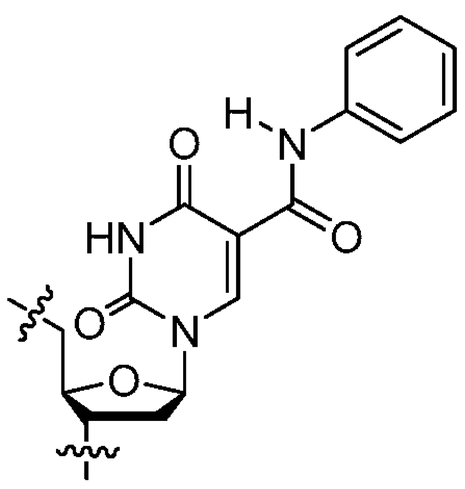
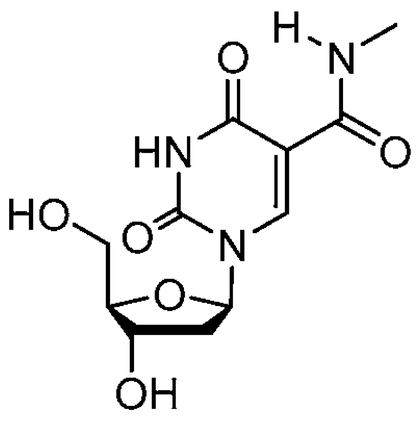
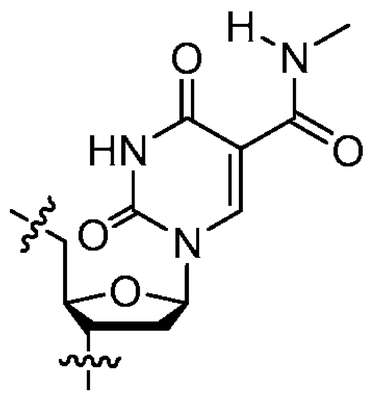
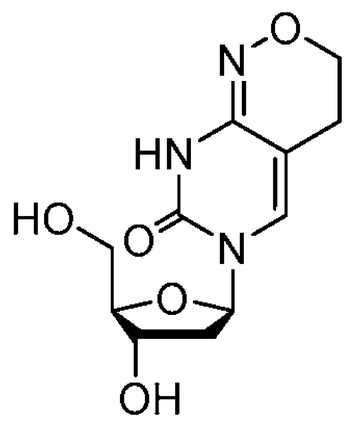
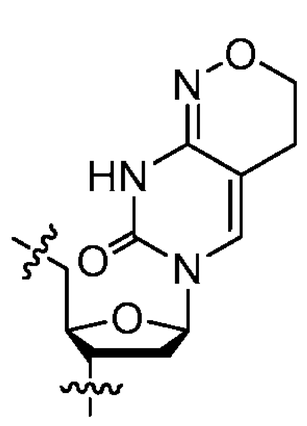
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b001U (which when utilized for a nucleoside refers to

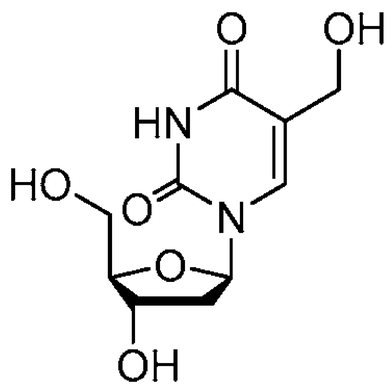
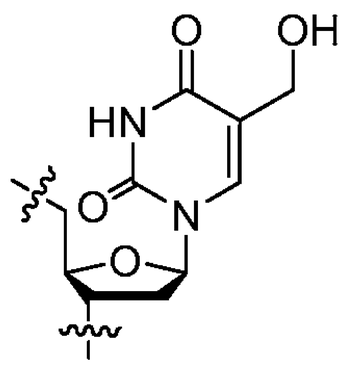


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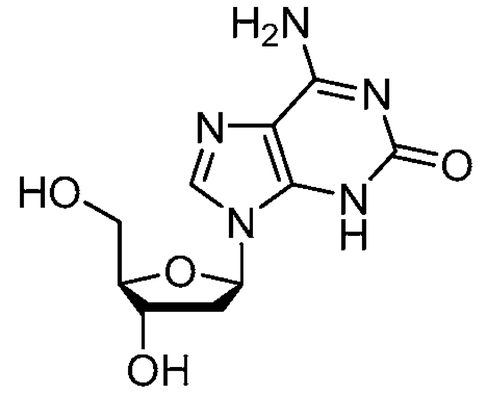


in an oligonucleotide chain unless specified otherwise). In some embodiments, it

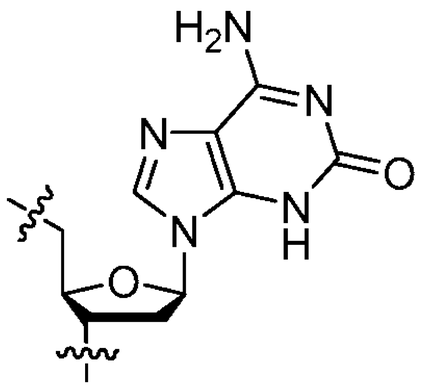
is b002U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b003U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b004U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b005U (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b006U (which when utilized for a nucleoside refers to or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b007U (which when utilized for a nucleoside refers to

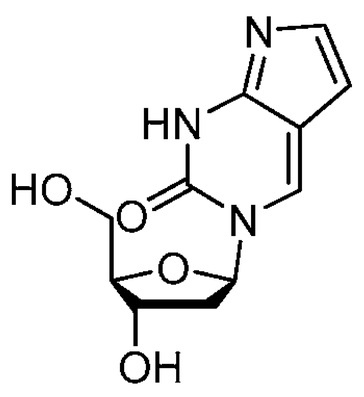
or in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b001G (which when utilized for a nucleoside refers to



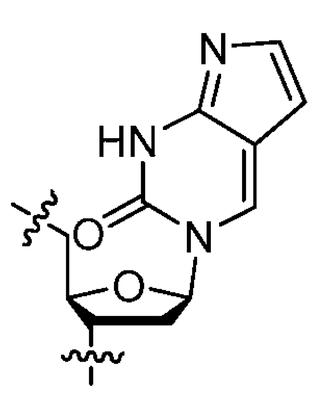
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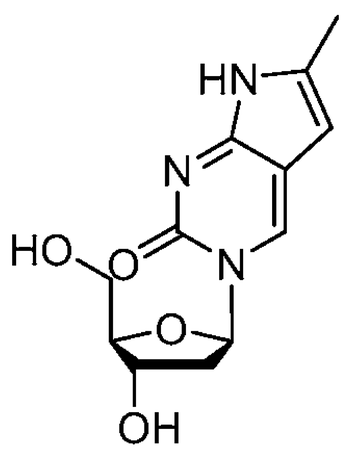
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b002C (which when utilized for a nucleoside refers to



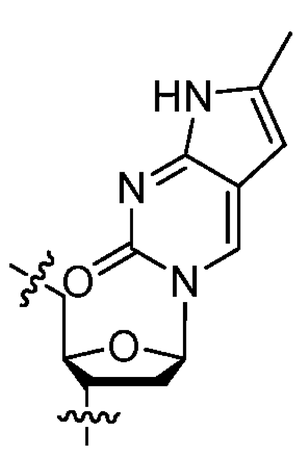
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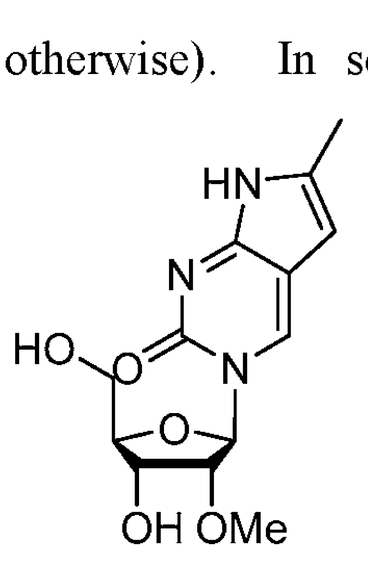
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b003C (which when utilized for a nucleoside refers to



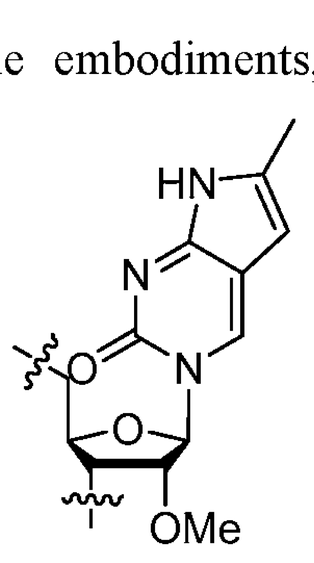
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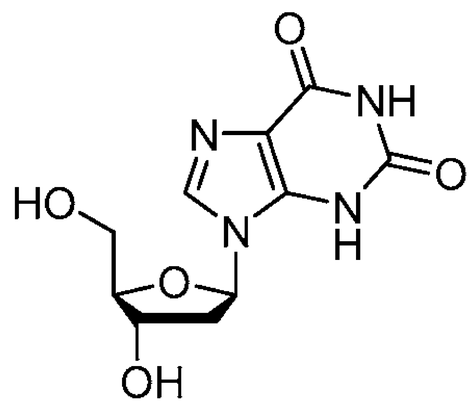
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b003mC (which when utilized for a nucleoside refers to



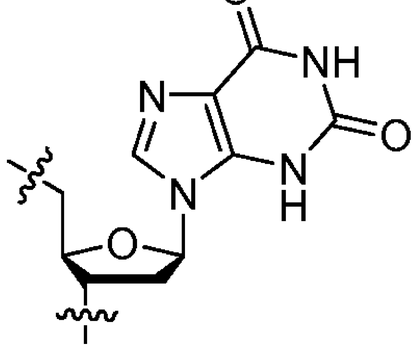
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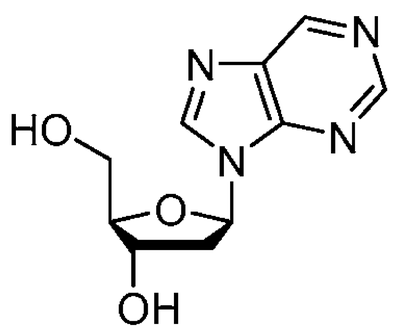
in an oligonucleotide chain unless specified otherwise). In some



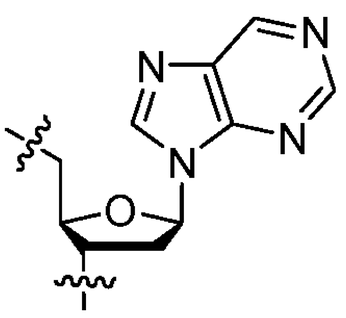
embodiments, it is b002I (which when utilized for a nucleoside refers to



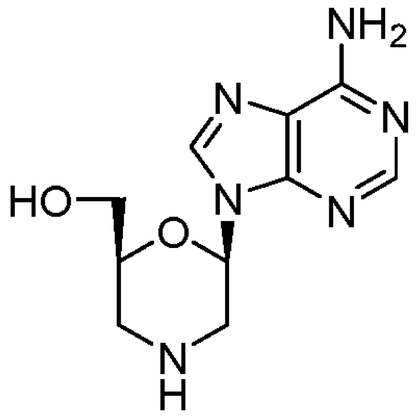
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is b003I (which when utilized for a nucleoside refers to



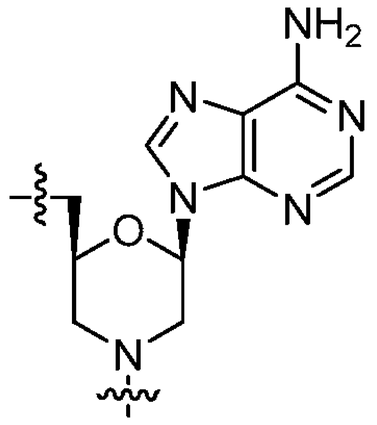
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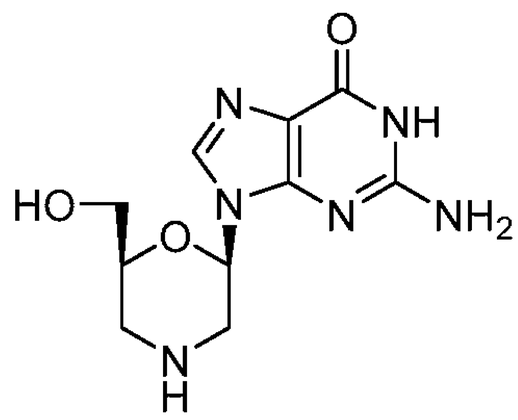
in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Asm01 (which when utilized for a nucleoside refers to



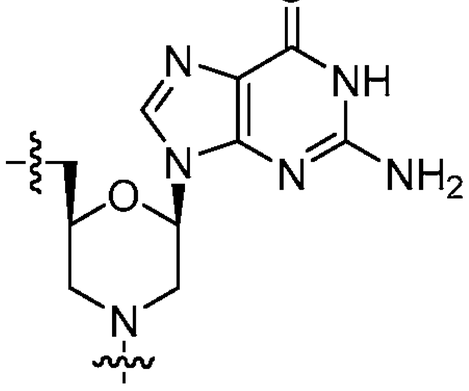
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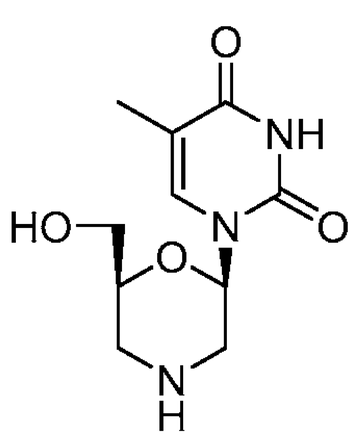
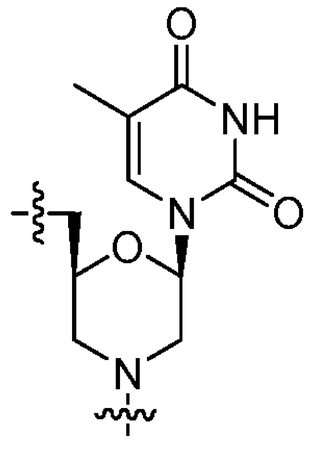
in an oligonucleotide chain unless specified otherwise; in some embodiments, the nitrogen atom is bonded to a linkage phosphorus). In some embodiments, it is Gsm01 (which when utilized for a nucleoside refers to

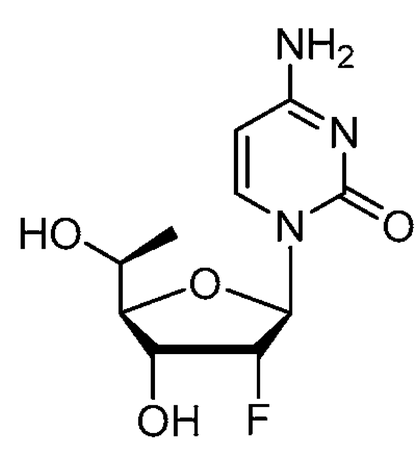
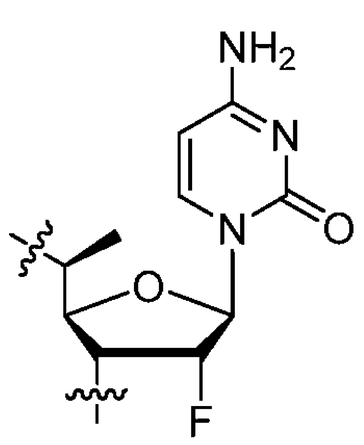
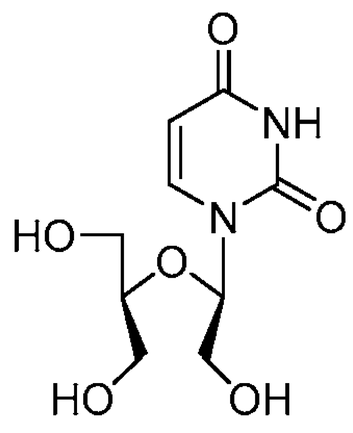
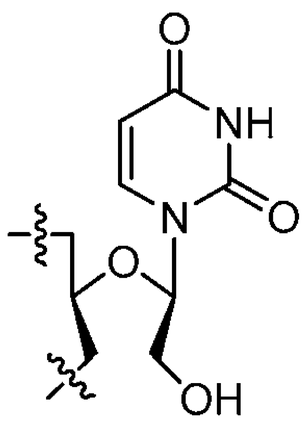
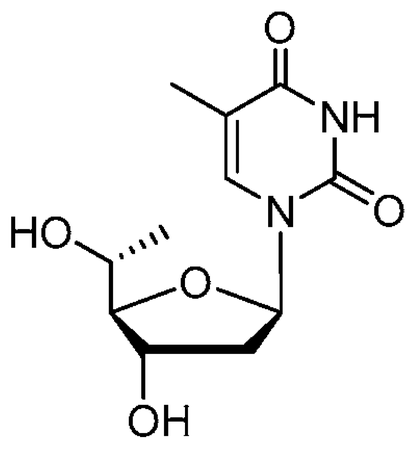
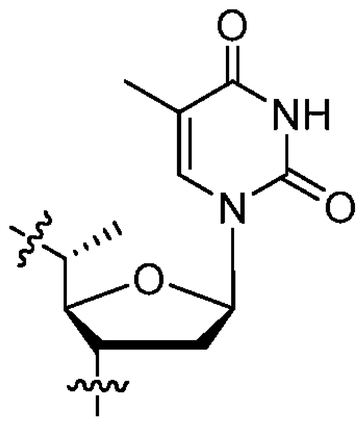
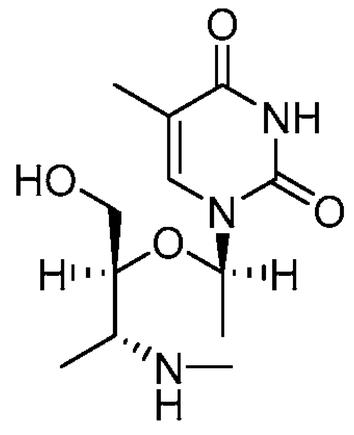


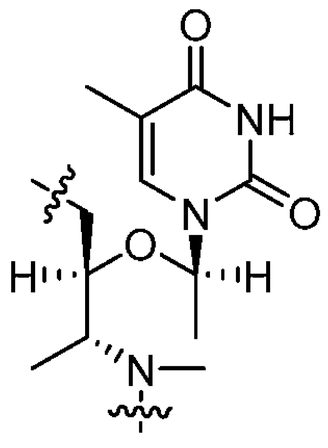
or



in an oligonucleotide chain unless specified otherwise; in some embodiments, the nitrogen atom is bonded to a linkage phosphorus). In some embodiments, it is Tsm01 (which when utilized

for a nucleoside refers to or in an oligonucleotide chain unless specified otherwise; in some embodiments, the nitrogen atom is bonded to a linkage phosphorus). In some embodiments, it is 5MsfC (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Usm04 (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is 5MRdT (which when utilized for a nucleoside refers to  or  in an oligonucleotide chain unless specified otherwise). In some embodiments, it is Tsm18 (which when utilized for a nucleoside refers to  or



in an oligonucleotide chain unless specified otherwise; in some embodiments, the nitrogen atom is bonded to a linkage phosphorus). In some embodiments, N_0 is abasic. In some embodiments, N_0 is L010.

[00546] In some embodiments, as demonstrated in various examples, certain modified nucleosides or nucleobases, e.g., b001A, b008U etc., can provide improved editing, e.g., when compared to dC at positions opposite to target adenosines. In some embodiments, it was observed that certain nucleosides, e.g., dC, b001A, b001rA, Csm15, b001C, etc. can provide improved adenosine editing efficiency when utilized at N_0 compared to a reference nucleoside (e.g., under comparable conditions including in otherwise identical oligonucleotides, assessed in identical or comparable assays, etc.). In some embodiments, N_0 is b001A. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b002A. In some embodiments, N_0 is b003A. In some embodiments, N_0 is b004I. In some embodiments, N_0 is b014I. In some embodiments, N_0 is b002G. In some embodiments, N_0 is dC. In some embodiments, N_0 is b001C. In some embodiments, N_0 is b009U. In some embodiments, N_0 is b010U. In some embodiments, N_0 is b011U. In some embodiments, N_0 is b012U. In some embodiments, N_0 is b013U. In some embodiments, N_0 is Csm04. In some embodiments, N_0 is Csm11. In some embodiments, N_0 is Csm12. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b009Csm11. In some embodiments, N_0 is b009Csm12. In some embodiments, N_0 is Gsm11. In some embodiments, N_0 is Gsm12. In some embodiments, N_0 is Tsm11. In some embodiments, N_0 is Tsm12. In some embodiments, a reference nucleoside is rU. In some embodiments, a reference nucleoside is dU. In some embodiments, a reference nucleoside is dT. In some embodiments, at N_0 position there is no nucleobase. In some embodiments, at N_0 position it is L010. In some embodiments, sugar of N_0 is sm15.

[00547] In some embodiments, replacing guanine with hypoxanthine at position -1 (e.g., replacing dG with dI) can provide improved editing. Certain data are provided in Figure 17 and others as examples.

[00548] In some embodiments, an oligonucleotide comprises 5'-$N_1N_0N_{-1}$-3' wherein each of N_1, N_0, and N_{-1} is independently a nucleoside as described herein. In some embodiments, an oligonucleotide comprises 5'-$N_2N_1N_0N_{-1}N_{-2}$-3' wherein each of N_2, N_1, N_0, N_{-1}, and N_{-2} is independently a nucleoside as described herein. In some embodiments, an oligonucleotide comprises 5'-$N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}$-3' wherein each of N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, and N_{-3} is independently a nucleoside as described herein. In some embodiments, an oligonucleotide comprises 5'-$N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}$-3' wherein each of N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, and N_{-4} is independently a nucleoside as described herein. In some embodiments, an oligonucleotide comprises 5'-$N_5N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}$-3' wherein each of N_5, N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, and N_{-5} is independently a nucleoside as described herein. In some embodiments, an oligonucleotide comprises 5'-

$N_6N_5N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}N_{-6}$-3' wherein each of N_6, N_5, N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a nucleoside as described herein. In some embodiments, N_n wherein n is a positive number, e.g., N_1, may also be referred to as N_{+1}. In some embodiments, such an oligonucleotide can form a duplex with a nucleic acid (e.g., a RNA nucleic acid) and can edit a target adenosine which is opposite to N_0. In some embodiments, N_{-6} is the last nucleoside of an oligonucleotide (counting from the 5'-end).

[00549] In some embodiments, an oligonucleotide comprises 5'-$N_2N_1N_0N_{-1}N_{-2}$-3', wherein each of N_2, N_1, N_0, N_{-1}, and N_{-2} is independently a nucleoside. In some embodiments, an oligonucleotide comprises 5'-$N_2N_1N_0N_{-1}N_{-2}$-3', wherein each of N_2, N_1, N_0, N_{-1}, and N_{-2} is independently a nucleoside. In some embodiments, an oligonucleotide comprises 5'-$N_2N_1N_0N_{-1}N_{-2}$-3', wherein each of N_2, N_1, N_0, N_{-1}, and N_{-2} is independently a nucleoside, N_0 is opposite to a target adenosine, and each two of N_2, N_1, N_0, N_{-1}, and N_{-2} that are next to each other, as those skilled in the art will appreciate, independently bond to an internucleotidic linkage as described herein. In some embodiments, one or more or all of N_1, N_0, and N_{-1} independently have a natural RNA sugar. In some embodiments, one or more or all of N_1, N_0, and N_{-1} independently have a natural DNA sugar. In some embodiments, the sugar of each of N_1, N_0, and N_{-1} is independently a natural DNA sugar or a 2'-F modified sugar. In some embodiments, the sugar of each of N_1, N_0, and N_{-1} is independently a natural DNA sugar. In some embodiments, the sugar of N_1 is a 2'-modified sugar, and the sugar of each of N_0 and N_{-1} is independently a natural DNA sugar. In some embodiments, the sugar of N_1 is a 2'-F sugar, and the sugar of each of N_0 and N_{-1} is independently a natural DNA sugar. In some embodiments, the sugar of N_1 is a modified sugar. In some embodiments, the sugar of N_1 is a 2'-F modified sugar. In some embodiments, the sugar of N_1 is a natural DNA sugar. In some embodiments, the sugar of N_1 is a natural RNA sugar. In some embodiments, the sugar of N_0 is not a modified sugar. In some embodiments, the sugar of N_0 is not a 2'-modified sugar. In some embodiments, the sugar of N_0 is not a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, the sugar of N_0 is not a 2'-F modified sugar. In some embodiments, the sugar of N_0 is not a 2'-OMe modified sugar. In some embodiments, the sugar of N_0 is a natural DNA or RNA sugar. In some embodiments, the sugar of N_0 is a natural DNA sugar. In some embodiments, the sugar of N_0 is a natural RNA sugar. In some embodiments, the sugar of N_{-1} is not a modified sugar. In some embodiments, the sugar of N_{-1} is not a 2'-modified sugar. In some embodiments, the sugar of N_{-1} is not a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, the sugar of N_{-1} is not a 2'-F modified sugar. In some embodiments, the sugar of N_{-1} is not a 2'-OMe modified sugar. In some embodiments, the sugar of N_{-1} is a natural DNA or RNA sugar. In some embodiments, the sugar of N_{-1} is a natural DNA sugar. In some embodiments, the sugar of N_{-1} is a natural RNA sugar. In some embodiments, each of N_1, N_0 and N_{-1} independently has a natural RNA sugar. In some embodiments, each of N_1, N_0 and N_{-1} independently has a natural DNA sugar. In some embodiments, N_1 has a 2'-F modified sugar, and each of N_0 and N_{-1} independently has a natural DNA or RNA sugar. In some embodiments, N_1 has a 2'-F modified sugar, and each of N_0 and N_{-1} independently has a natural DNA sugar(e.g., WV-22434). In some embodiments, two of N_1, N_0, and N_{-1} independently have a natural DNA or RNA sugar. In some embodiments,

two of N_1, N_0, and N_{-1} independently have a natural DNA sugar. In some embodiments, each of N_1 and N_0 independently has a 2'-F modified sugar, and N_{-1} is a natural DNA sugar.

[00550] In some embodiments, such oligonucleotides provide high editing levels. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently *R*p. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently an *R*p phosphorothioate internucleotidic linkage. In some embodiments, each of the two internucleotidic linkages bonded to N_{-1} is independently an *R*p phosphorothioate internucleotidic linkage, and each other phosphorothioate internucleotidic linkage in an oligonucleotide, if any, is independently *S*p. In some embodiments, a 5' internucleotidic linkage bonded to N_1 is *R*p. In some embodiments, an internucleotidic linkage bonded to N_1 and N_0 (i.e., a 3' internucleotidic linkage bonded to N_1) is *R*p. In some embodiments, an internucleotidic linkage bonded to N_{-1} and N_0 is *R*p. In some embodiments, a 3' internucleotidic linkage bonded to N_{-1} is *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 or N_1 is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_0 or N_{-1} is independently *R*p. In some embodiments, each internucleotidic linkage bonded to N_1 is independently *R*p. In some embodiments, each *R*p internucleotidic linkage is independently an *R*p phosphorothioate internucleotidic linkage. In some embodiments, each other chirally controlled phosphorothioate internucleotidic linkage in an oligonucleotide is independently *S*p. In some embodiments, the internucleotidic linkage between N_0N_{-1} is *R*p. In some embodiments, the internucleotidic linkage between N_0N_{-1} is *R*p phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage between $N_{-1}N_{-2}$ is *R*p. In some embodiments, the internucleotidic linkage between $N_{-1}N_{-2}$ is *R*p phosphorothioate internucleotidic linkage. In some embodiments, all internucleotidic linkages bonded to N_1, N_0, and N_{-1} are independently *S*p. In some embodiments, all internucleotidic linkages bonded to N_1, N_0, and N_{-1} are independently *S*p phosphorothioate internucleotidic linkages. In some embodiments, all internucleotidic linkages bonded to N_2, N_1, N_0, N_{-1}, and N_{-2} are independently *S*p. In some embodiments, all internucleotidic linkages bonded to N_2, N_1, N_0, N_{-1}, and N_{-2} are independently *S*p phosphorothioate internucleotidic linkages. In some embodiments, both internucleotidic linkage bonded to N_1 are independently *S*p (e.g., *S*p phosphorothioate internucleotidic linkages). In some embodiments, an internucleotidic linkage between N_1 and N_0 is *S*p (e.g., a *S*p phosphorothioate internucleotidic linkage). In some embodiments, an internucleotidic linkage between N_{-1} and N_0 is *S*p (e.g., a *S*p phosphorothioate internucleotidic linkage). In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is a neutral internucleotidic linkage. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is n001. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is not chirally controlled. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is chirally controlled. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is *R*p. In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is *S*p. In some embodiments, N_2 comprises a modified sugar. In some embodiments, N_{-2} comprises a modified sugar. In some embodiments,

each of N_2 and N_{-2} independently comprises a modified sugar. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, a modified sugar is 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modified sugar is 2'-OMe modified sugar. In some embodiments, a 2'-modified sugar is 2'-MOE modified sugar. In some embodiments, a modified sugar is a bicyclic sugar, e.g., a LNA sugar, a cEt sugar, etc.

[00551] In some embodiments, to the 3'-side of a nucleoside opposite to a target adenosine (e.g., N_0) there are at least 2, 3, 4, 5, 6, 7, 8, 9 or more nucleosides (e.g., 2-30, 3-30, 4-30, 5-30, 2-20, 3-20, 4-20, 5-20, 2-15, 3-15, 4-15, 5-15, 2-10, 3-10, 4-10, 5-10, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc., "3'-side nucleosides"). In some embodiments, there are at least 2 3'-side nucleosides. In some embodiments, there are at least 3 3'-side nucleosides. In some embodiments, there are at least 4 3'-side nucleosides. In some embodiments, there are at least 5 3'-side nucleosides (e.g., an oligonucleotide comprising 5'-$N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}$-3', wherein each of N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, and N_{-5} is independently a nucleoside). In some embodiments, there are at least 6 3'-side nucleosides (e.g., an oligonucleotide comprising 5'-$N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}N_{-6}$-3', wherein each of N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a nucleoside). In some embodiments, there are at least 7 3'-side nucleosides. In some embodiments, there are at least 8 3'-side nucleosides. In some embodiments, there are at least 9 3'-side nucleosides. In some embodiments, there are at least 10 3'-side nucleosides. In some embodiments, there are 2 3'-side nucleosides. In some embodiments, there are 3 3'-side nucleosides. In some embodiments, there are 4 3'-side nucleosides. In some embodiments, there are 5 3'-side nucleosides. In some embodiments, there are 6 3'-side nucleosides. In some embodiments, there are 7 3'-side nucleosides. In some embodiments, there are 8 3'-side nucleosides. In some embodiments, there are 9 3'-side nucleosides. In some embodiments, there are 10 3'-side nucleosides. In some embodiments, to the 5'-side of a nucleoside opposite to a target adenosine (e.g., N_0) there are at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more nucleosides (e.g., 15-50, 20-50, 21-50, 22-50, 23-50, 24-50, 25-50, 26-50, 27-50, 28-50, 29-50, 30-50, 15-40, 20-40, 21-40, 22-40, 23-40, 24-40, 25-40, 26-40, 27-40, 28-40, 29-40, 30-40, 15-30, 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 26-30, 27-30, 28-30, 29-30, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, there are at least 15 5'-side nucleosides. In some embodiments, there are at least 16 5'-side nucleosides. In some embodiments, there are at least 17 5'-side nucleosides. In some embodiments, there are at least 18 5'-side nucleosides. In some embodiments, there are at least 19 5'-side nucleosides. In some embodiments, there are at least 20 5'-side nucleosides. In some embodiments, there are at least 21 5'-side nucleosides. In some embodiments, there are at least 22 5'-side nucleosides. In some embodiments, there are at least 23 5'-side nucleosides. In some embodiments, there are at least 24 5'-side nucleosides. In some embodiments, there are at least 25 5'-side nucleosides. In some embodiments, there are at least 26 5'-side nucleosides. In some embodiments, there are at least 27 5'-side nucleosides. In some embodiments, there are at least 28 5'-side nucleosides. In some embodiments, there are at least 29 5'-side nucleosides. In some embodiments, there are at least 30 5'-side nucleosides. In some embodiments, there are 15 5'-side nucleosides. In some embodiments, there are 16 5'-side nucleosides. In

some embodiments, there are 17 5’-side nucleosides. In some embodiments, there are 18 5’-side nucleosides. In some embodiments, there are 19 5’-side nucleosides. In some embodiments, there are 20 5’-side nucleosides. In some embodiments, there are 21 5’-side nucleosides. In some embodiments, there are 22 5’-side nucleosides. In some embodiments, there are 23 5’-side nucleosides. In some embodiments, there are 24 5’-side nucleosides. In some embodiments, there are 25 5’-side nucleosides. In some embodiments, there are 26 5’-side nucleosides. In some embodiments, there are 27 5’-side nucleosides. In some embodiments, there are 28 5’-side nucleosides. In some embodiments, there are 29 5’-side nucleosides. In some embodiments, there are 30 5’-side nucleosides. In some embodiments, there are at least 4 3’-side nucleosides and at least 22 5’-side nucleosides. In some embodiments, there are at least 4 3’-side nucleosides and at least 23 5’-side nucleosides. In some embodiments, there are at least 4 3’-side nucleosides and at least 24 5’-side nucleosides. In some embodiments, there are at least 4 3’-side nucleosides and at least 25 5’-side nucleosides. In some embodiments, there are at least 5 3’-side nucleosides and at least 22 5’-side nucleosides. In some embodiments, there are at least 5 3’-side nucleosides and at least 23 5’-side nucleosides. In some embodiments, there are at least 5 3’-side nucleosides and at least 24 5’-side nucleosides. In some embodiments, there are at least 5 3’-side nucleosides and at least 25 5’-side nucleosides. In some embodiments, there are at least 6 3’-side nucleosides and at least 21 5’-side nucleosides. In some embodiments, there are at least 6 3’-side nucleosides and at least 22 5’-side nucleosides. In some embodiments, there are at least 6 3’-side nucleosides and at least 23 5’-side nucleosides. In some embodiments, there are at least 6 3’-side nucleosides and at least 24 5’-side nucleosides. In some embodiments, there are at least 7 3’-side nucleosides and at least 20 5’-side nucleosides. In some embodiments, there are at least 7 3’-side nucleosides and at least 21 5’-side nucleosides. In some embodiments, there are at least 7 3’-side nucleosides and at least 22 5’-side nucleosides. In some embodiments, there are at least 7 3’-side nucleosides and at least 23 5’-side nucleosides. In some embodiments, there are at least 8 3’-side nucleosides and at least 19 5’-side nucleosides. In some embodiments, there are at least 8 3’-side nucleosides and at least 20 5’-side nucleosides. In some embodiments, there are at least 8 3’-side nucleosides and at least 21 5’-side nucleosides. In some embodiments, there are at least 8 3’-side nucleosides and at least 22 5’-side nucleosides. In some embodiments, there are at least 9 3’-side nucleosides and at least 18 5’-side nucleosides. In some embodiments, there are at least 9 3’-side nucleosides and at least 19 5’-side nucleosides. In some embodiments, there are at least 9 3’-side nucleosides and at least 20 5’-side nucleosides. In some embodiments, there are at least 9 3’-side nucleosides and at least 21 5’-side nucleosides. In some embodiments, there are at least 10 3’-side nucleosides and at least 17 5’-side nucleosides. In some embodiments, there are at least 10 3’-side nucleosides and at least 18 5’-side nucleosides. In some embodiments, there are at least 10 3’-side nucleosides and at least 19 5’-side nucleosides. In some embodiments, there are at least 10 3’-side nucleosides and at least 20 5’-side nucleosides. In some embodiments, there are at least 11 3’-side nucleosides and at least 16 5’-side nucleosides. In some embodiments, there are at least 11 3’-side nucleosides and at least 17 5’-side nucleosides. In some embodiments, there are at least 11 3’-side nucleosides and at least 18 5’-side nucleosides. In some

embodiments, there are at least 11 3'-side nucleosides and at least 19 5'-side nucleosides. In some embodiments, there are at least 12 3'-side nucleosides and at least 15 5'-side nucleosides. In some embodiments, there are at least 12 3'-side nucleosides and at least 16 5'-side nucleosides. In some embodiments, there are at least 12 3'-side nucleosides and at least 17 5'-side nucleosides. In some embodiments, there are at least 12 3'-side nucleosides and at least 18 5'-side nucleosides. In some embodiments, there are at least 13 3'-side nucleosides and at least 14 5'-side nucleosides. In some embodiments, there are at least 13 3'-side nucleosides and at least 15 5'-side nucleosides. In some embodiments, there are at least 13 3'-side nucleosides and at least 16 5'-side nucleosides. In some embodiments, there are at least 13 3'-side nucleosides and at least 17 5'-side nucleosides. In some embodiments, certain useful lengths of 5'-sides and/or 3'-sides and/or positioning of nucleosides opposite to target adenosines (e.g., C of UCI in oligonucleotides described in (a), Figure 2) are described in Figure 2 and Figure 3.

[00552] As described herein, wherein modifications may be utilized for N_1, including sugar modifications, nucleobase modifications, etc. In some embodiments, N_1 contains a natural DNA sugar. In some embodiments, N_1 contains a natural RNA sugar. In some embodiments, N_1 contains a modified sugar as described herein. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, a modified sugar is a 2'-F modified sugar. In some embodiments, a modified sugar is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a modified sugar is a 2'-OMe modified sugar. In some embodiments, a modified sugar is a 2'-MOE modified sugar. In some embodiments, a sugar is a UNA sugar. In some embodiments, a sugar is a GNA sugar. In some embodiments, sugar of N_1 is sm01. In some embodiments, it is sm11. In some embodiments, it is sm12. In some embodiments, it is sm18. In some embodiments, a modified sugar, e.g., a 2'-F modified sugar, or a DNA sugar provides higher editing efficiency when administered to a system (e.g., a cell, a tissue, an organism, etc.) compared to a reference sugar (e.g., a natural RNA sugar, a different modified sugar, etc.). In some embodiments, N_1 contains a natural nucleobase, e.g., U. In some embodiments, N_1 contains a modified nucleobase as described herein. In some embodiments, nucleobase of N_1 is A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp. In some embodiments, nucleobase of N_1 is T. In some embodiments, it is U. In some embodiments, it is b002A. In some embodiments, it is b003A. In some embodiments, it is b008U. In some embodiments, it is b010U. In some embodiments, it is b011U. In some embodiments, it is b012U. In some embodiments, it is b001C. In some embodiments, it is b004C. In some embodiments, it is b007C. In some embodiments, it is b008C. In some embodiments, N_1 is a natural nucleoside. In some embodiments, N_1 is a modified nucleoside. In some embodiments, N_1 is fU, dU, fA, dA, fT, dT, fC, dC, fG, dG, dI, fI, aC, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b010U, b011U, b012U, b013U, b001A, b001rA, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b003mC, b004C, b005C, b006C, b007C, b008C, b002I, b003I, b004I, b014I,

Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm04, Csm11, Gsm11, Tsm11, b009Csm11, b009Csm12, Gsm12, Tsm12, Csm12, rCsm13, rCsm14, Csm15, Csm16, Csm17, L034, zdnp, and Tsm18. In some embodiments, N_1 is fU, dU, fA, dA, fT, dT, fC, dC, fG, dG, dI, or fI. In some embodiments, N_1 is fU, dU, fA, dA, fT, dT, fC, dC, fG, or dG. In some embodiments, N_1 is dT. In some embodiments, N_1 is b001A. In some embodiments, N_1 is b002A. In some embodiments, N_1 is b003A. In some embodiments, N_1 is fU. In some embodiments, N_1 is b008U. In some embodiments, N_1 is b001C. In some embodiments, N_1 is b004C. In some embodiments, N_1 is b007C. In some embodiments, N_1 is b008C. In some embodiments, N_1 is b001U. In some embodiments, N_1 is b008U. In some embodiments, N_1 is b010U. In some embodiments, N_1 is b011U. In some embodiments, N_1 is b012U. In some embodiments, N_1 is Csm11. In some embodiments, N_1 is Gsm11. In some embodiments, N_1 is Tsm11. In some embodiments, N_1 is b009Csm11. In some embodiments, N_1 is Csm12. In some embodiments, N_1 is Gsm12. In some embodiments, N_1 is Tsm12. In some embodiments, N_1 is b009Csm12. In some embodiments, N_1 is Gsm01. In some embodiments, N_1 is Tsm01. In some embodiments, N_1 is Csm17. In some embodiments, N_1 is Tsm18. In some embodiments, N_1 is b014I. In some embodiments, N_1 is abasic. In some embodiments, N_1 is L010. As described herein, at position N_1 in some embodiments, it is a match when an oligonucleotide forms a duplex with a nucleic acid (e.g., its target transcript for adenosine editing). In some embodiments, it is a mismatch. In some embodiments, it is a wobble. In some embodiments, N_1 is bonded to a natural phosphate linkage. In some embodiments, N_1 is bonded to a modified internucleotidic linkage as described herein, in various embodiments, with defined stereochemistry. In some embodiments, N_1 is bonded to a natural phosphate linkage and a modified internucleotidic linkage. In some embodiments, N_1 is bonded to two natural phosphate linkages. In some embodiments, N_1 is bonded to two modified internucleotidic linkages, each of which may be independently and optionally stereocontrolled and may be *R*p or *S*p.

[00553] As described herein, wherein modifications may be utilized for N_{-1}, including sugar modifications, nucleobase modifications, etc. In some embodiments, N_{-1} contains a natural DNA sugar. In some embodiments, N_{-1} contains a natural RNA sugar. In some embodiments, N_{-1} contains a modified sugar as described herein. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, a modified sugar is a 2'-F modified sugar. In some embodiments, a modified sugar is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a modified sugar is a 2'-OMe modified sugar. In some embodiments, a modified sugar is a 2'-MOE modified sugar. In some embodiments, a sugar is a UNA sugar. In some embodiments, a sugar is a GNA sugar. In some embodiments, sugar of N_{-1} is sm01. In some embodiments, it is sm11. In some embodiments, it is sm12. In some embodiments, it is sm18. In some embodiments, a modified sugar, e.g., a 2'-F modified sugar, or a DNA sugar provides higher editing efficiency when administered to a system (e.g., a cell, a tissue, an organism, etc.) compared to a reference sugar (e.g., a natural RNA sugar, a different modified sugar, etc.). In some embodiments, N_{-1} contains a natural nucleobase, e.g., U. In some embodiments, N_{-1} contains a modified nucleobase as described herein. In some embodiments, nucleobase of N_{-1} is A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U,

b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp. In some embodiments, nucleobase of N_{-1} is T. In some embodiments, it is U. In some embodiments, it is b001A. In some embodiments, it is b002A. In some embodiments, it is b003A. In some embodiments, it is b008U. In some embodiments, it is b011U. In some embodiments, it is b012U. In some embodiments, it is b001C. In some embodiments, it is b004C. In some embodiments, it is b007C. In some embodiments, it is b008C. In some embodiments, it is b009C. In some embodiments, it is b002G. In some embodiments, it is b014I. In some embodiments, N_{-1} is a natural nucleoside. In some embodiments, N_{-1} is a modified nucleoside. In some embodiments, N_{-1} is fU, dU, fA, dA, fT, dT, fC, dC, fG, dG, dI, fI, aC, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b010U, b011U, b012U, b013U, b001A, b001rA, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b003mC, b004C, b005C, b006C, b007C, b008C, b002I, b003I, b004I, b014I, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm04, Csm11, Gsm11, Tsm11, b009Csm11, b009Csm12, Gsm12, Tsm12, Csm12, rCsm13, rCsm14, Csm15, Csm16, Csm17, L034, zdnp, and Tsm18. In some embodiments, N_{-1} is fU, dU, fA, dA, fT, dT, fC, dC, fG, dG, dI, or fI. In some embodiments, N_{-1} is fU, dU, fA, dA, fT, dT, fC, dC, fG, or dG. In some embodiments, N_{-1} is dI. In some embodiments, N_{-1} is rI. In some embodiments, N_{-1} is dT. In some embodiments, N_{-1} is b001A. In some embodiments, N_{-1} is b002A. In some embodiments, N_{-1} is b003A. In some embodiments, N_{-1} is fU. In some embodiments, N_{-1} is b001C. In some embodiments, N_{-1} is b004C. In some embodiments, N_{-1} is b007C. In some embodiments, N_{-1} is b008C. In some embodiments, N_{-1} is b009Csm12. In some embodiments, N_{-1} is b001U. In some embodiments, N_{-1} is b008U. In some embodiments, N_{-1} is b010U. In some embodiments, N_{-1} is b011U. In some embodiments, N_{-1} is b012U. In some embodiments, N_{-1} is Csm11. In some embodiments, N_{-1} is b009Csm11. In some embodiments, N_{-1} is Gsm11. In some embodiments, N_{-1} is Tsm11. In some embodiments, N_{-1} is Csm12. In some embodiments, N_{-1} is b009Csm12. In some embodiments, N_{-1} is Gsm12. In some embodiments, N_{-1} is Tsm12. In some embodiments, N_{-1} is Gsm01. In some embodiments, N_{-1} is Tsm01. In some embodiments, N_{-1} is Tsm18. In some embodiments, N_{-1} is abasic. In some embodiments, N_{-1} is L010. In some embodiments, N_{-1} is Csm17. In some embodiments, N_{-1} is b002G. In some embodiments, N_{-1} is b014I. As described herein, at position N_{-1} in some embodiments, it is a match when an oligonucleotide forms a duplex with a nucleic acid (e.g., its target transcript for adenosine editing). In some embodiments, it is a mismatch. In some embodiments, it is a wobble. In some embodiments, N_{-1} is bonded to a natural phosphate linkage. In some embodiments, N_{-1} is bonded to a modified internucleotidic linkage as described herein, in various embodiments, with defined stereochemistry. In some embodiments, N_{-1} is bonded to a natural phosphate linkage and a modified internucleotidic linkage. In some embodiments, N_{-1} is bonded to two natural phosphate linkages. In some embodiments, N_{-1} is bonded to two modified internucleotidic linkages, each of which may be independently and optionally stereocontrolled and may be *R*p or *S*p.

[00554] In some embodiments, N_2 contains a natural sugar. In some embodiments, sugar of N_2 is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar.

In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00555] In some embodiments, an internucleotidic linkage between N_1 and N_2 is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00556] In some embodiments, N_3 contains a natural sugar. In some embodiments, sugar of N_3 is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00557] In some embodiments, an internucleotidic linkage between N_2 and N_3 is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001. In some embodiments, N_4 contains a natural sugar. In some embodiments, sugar of N_4 is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00558] In some embodiments, an internucleotidic linkage between N_3 and N_4 is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00559] In some embodiments, N_5 contains a natural sugar. In some embodiments, sugar of N_5 is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar.

In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00560] In some embodiments, an internucleotidic linkage between N_4 and N_5 is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00561] In some embodiments, N_6 contains a natural sugar. In some embodiments, sugar of N_6 is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00562] In some embodiments, an internucleotidic linkage between N_5 and N_6 is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00563] As described herein, an oligonucleotide, or a portion thereof, e.g., a first domain, a second domain, etc., may comprise or consist of one or more, e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc. blocks, each of which independently comprises one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-10, 1-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, etc.) sugars, wherein each sugar in a block share the same structure. In some embodiments, an oligonucleotide, or a portion thereof, e.g., a first domain, a second domain, etc., may comprise or consist of one or more, e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc. blocks, each of which independently comprises one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-10, 1-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, etc.) sugars, wherein each sugar in a block is the same modified sugar. In some embodiments, each block independently contains 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, sugars. In some embodiments, each block independently contains 1-5 sugars. In some embodiments, each block independently contains 1, 2, or 3 sugars. In some embodiments, one or more blocks, e.g., 1-15, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,

15, 16, 17, 18, 19, 20 or more, independently contain two or three or more sugars. In some embodiments, one or more blocks, e.g., 1-15, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, independently contain two or three sugars. In some embodiments, about or at least about 30%, 40% or 50% blocks in an oligonucleotide or a portion thereof independently contains two or more (e.g., two or three) sugars. In some embodiments, about 50% blocks in an oligonucleotide of a first domain independently contains two or more (e.g., two or three) sugars. In some embodiments, a block is a 2'-F block wherein each sugar in the block is a 2'-F modified block. In some embodiments, a block is a 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic wherein each sugar in the block is the same 2'-OR modified sugar. In some embodiments, a block is a 2'-OMe block. In some embodiments, a block is a 2'-MOE block. In some embodiments, a block is a bicyclic sugar block wherein each sugar in the block is the same bicyclic sugar (e.g., a LNA sugar, cEt, etc.). In some embodiments, two or more blocks are 2'-F blocks. In some embodiments, every other block is a 2'-F block. In some embodiments, each 2'-F block independently contains no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 sugars. In some embodiments, a 2'-F block contains no more than 5 sugars. In some embodiments, a 2'-F block contains no more than 4 sugars. In some embodiments, a 2'-F block contains no more than 3 sugars. In some embodiments, between every two 2'-F blocks in an oligonucleotide or a portion thereof there is at least one 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic or one bicyclic sugar block. In some embodiments, between every two 2'-F blocks in a portion there is at least one 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic or one bicyclic sugar block. In some embodiments, between every two 2'-F blocks in an oligonucleotide there is at least one 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, between every two 2'-F blocks in a first domain there is at least one 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, between every two 2'-F blocks in a first domain there is at least one 2'-OMe block. In some embodiments, between two 2'-F blocks in a first domain there is a 2'-OMe block. In some embodiments, between two 2'-F blocks in a first domain there is a 2'-MOE block. In some embodiments, between two 2'-F blocks in a first domain there is a 2'-MOE block and 2'-OMe block. In some embodiments, between two 2'-F blocks in a first domain there is a 2'-MOE block and 2'-OMe block and no 2'-F block. In some embodiments, each 2'-F block is independently bonded to a 2'-OR block wherein R is C_{1-6} aliphatic or a bicyclic sugar block. In some embodiments, each 2'-F block is independently bonded to a 2'-OR block wherein R is C_{1-6} aliphatic. In some embodiments, each block a 2'-F block bonds to is independently a 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar block. In some embodiments, each block a 2'-F block bonds to is independently a 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each block in a first domain that a 2'-F block in a first domain bonds to is independently a 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar block. In some embodiments, each block in a first domain that a 2'-F block in a first domain bonds to is independently a 2'-OR block wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each block in a first domain that a 2'-OR block wherein R is C_{1-6} aliphatic or a bicyclic sugar block bonds is independently a 2'-F block of a different 2'-OR block wherein R is C_{1-6} aliphatic or a bicyclic

sugar block. In some embodiments, each block in a first domain that a 2'-OR block wherein R is C_{1-6} aliphatic bonds is independently a 2'-F block of a different 2'-OR block wherein R is C_{1-6} aliphatic. In some embodiments, a 2'-OR block is a 2'-OMe block. In some embodiments, a 2'-OR block is a 2'-MOE block. In some embodiments, at least one block is a 2'-OMe block. In some embodiments, about or about at least 2, 3, 4, or 5 blocks are independently 2'-OMe block. In some embodiments, at least one block is a 2'-MOE block. In some embodiments, about or about at least 2, 3, 4, or 5 blocks are independently 2'-MOE block. In some embodiments, in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OMe block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-MOE block. In some embodiments, in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OMe block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-MOE block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-F block. In some embodiments, in a first domain there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OMe block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-MOE block. In some embodiments, in a first domain there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OMe block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-F block. In some embodiments, in a first domain there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-F block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-MOE block. In some embodiments, in a first domain there are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-OMe block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more) 2'-MOE block and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-F block. In some embodiments, in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., percentage of 2'-F modified sugars is about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, and percentage of 2'-OR modified sugars each of which is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic is about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80%. In some embodiments, in a first domain percentage of 2'-F modified sugars is about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, and percentage of 2'-OR modified sugars each of which is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic is about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80%. In some embodiments, the difference between the percentage of 2'-F modified sugars and the percentage of 2'-OR modified sugars each of which is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic is less than about 50%, 40%, 30%, 20%, or 10% (calculated by subtracting the smaller of the two percentages from the larger of the two percentages). In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar.

[00564] For example, in some embodiments, sugar of each of N_2, N_5, and N_6 is independently a 2'-F modified sugar, and sugar of each of N_3 and N_4 is independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, sugar of each of N_2, N_5, and N_6 is independently a 2'-F

modified sugar, and sugar of each of N_3 and N_4 is independently a 2'-OR modified sugar. In some embodiments, sugar of each of N_2, N_5, and N_6 is independently a 2'-F modified sugar, and sugar of each of N_3 and N_4 is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, sugar of each of N_2, N_5, and N_6 is independently a 2'-F modified sugar, and sugar of each of N_3 and N_4 is independently a 2'-OMe modified sugar. In some embodiments, at least one sugar is a 2'-MOE modified sugar. In some embodiments, sugar of N_3 is a 2'-MOE modified sugar. In some embodiments, sugar of N_3 is a 2'-OMe modified sugar. In some embodiments, sugar of N_4 is a 2'-MOE modified sugar. In some embodiments, sugars of both N_3 and N_4 are 2'-MOE modified sugar. In some embodiments, N_2 forms a 2'-F block. In some embodiments, N_3 and N_4 forms a 2'-OMe block. In some embodiments, N_3 and N_4 forms a 2'-MOE block. In some embodiments, N_5, N_6 and/or N_7 form a 2'-F block. As demonstrated herein, oligonucleotides comprising modified sugars, e.g., 2'-F modified sugars, 2'-OMe modified sugars, 2'-MOE modified sugars, etc., at various positions can provide, among other things, high levels of adenosine editing. For example, 2'-MOE modified sugars can be incorporated at various positions to provide oligonucleotides capable of adenosine editing; in some embodiments, sugar of N_1 is a 2'-MOE modified sugar; in some embodiments, sugar of N_2 is a 2'-MOE modified sugar; in some embodiments, sugar of N_3 is a 2'-MOE modified sugar; in some embodiments, sugar of N_4 is a 2'-MOE modified sugar; in some embodiments, sugar of N_5 is a 2'-MOE modified sugar; in some embodiments, sugar of N_6 is a 2'-MOE modified sugar; in some embodiments, sugar of N_7 is a 2'-MOE modified sugar; in some embodiments, sugar of N_8 is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-1} is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-2} is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-3} is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-4} is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-5} is a 2'-MOE modified sugar; in some embodiments, sugar of N_{-6} is a 2'-MOE modified sugar.

[00565] As described herein, various internucleotidic linkages may be utilized in oligonucleotides or portions thereof, e.g., first domains, second domains, etc. For example, various linkages may be utilized in first domains. In some embodiments, a first domain comprises one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more natural phosphate linkages. In some embodiments, a first domain comprises one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, modified internucleotidic linkages. In some embodiments, a first domain comprises one or more natural phosphate linkages and one or more modified internucleotidic linkages. In some embodiments, one or more modified internucleotidic linkages are phosphorothioate internucleotidic linkages. In some embodiments, each phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc. is *Sp*. In some embodiments, each phosphorothioate internucleotidic linkage in an oligonucleotide is *Sp*. In some embodiments, one or more modified internucleotidic linkages are independently non-negatively charged internucleotidic linkage. In some embodiments, one or more modified internucleotidic linkage. In some embodiments, one or more modified internucleotidic linkages are independently non-negatively charged internucleotidic linkage. In some embodiments, one or more modified

internucleotidic linkages are independently phosphoryl guanidine internucleotidic linkages. In some embodiments, each phosphoryl guanidine internucleotidic linkage is independently n001. In some embodiments, a first domain contains about 1-5, e.g., 1, 2, 3, 4, or 5 non-negatively charged internucleotidic linkages. In some embodiments, each of such non-negatively charged internucleotidic linkages are independently a phosphoryl guanidine internucleotidic linkage. In some embodiments, each of them is independently n001. In some embodiments, one or more of them are independently chirally controlled. In some embodiments, each of them is chirally controlled. In some embodiments, each of them is *R*p n001. In some embodiments, one or more sugars that are 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic are boned to natural phosphate linkages. In some embodiments, one or more 2'-OMe sugars are bonded to natural phosphate linkages. In some embodiments, one or more 2'-MOE sugars are bonded to natural phosphate linkages. In some embodiments, one or more 2'-F modified sugars are bonded to natural phosphate linkages. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-OMe modified sugars in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-MOE modified sugars in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic in a first domain, a second domain are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-OMe modified sugars in a first domain are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-MOE modified sugars in a first domain are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic in a first domain, a second domain are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 2'-OMe modified sugars in a first domain are independently bonded to a natural phosphate linkage. In some embodiments, about or at least about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 2'-MOE modified sugars in a first domain are independently bonded to a natural phosphate linkage. In some embodiments, one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more, natural phosphate linkage bonded to a 2'-F modified sugar are independently bonded to a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, each natural phosphate linkage bonded to a 2'-F modified sugar is independently bonded to a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more, natural phosphate linkages bonded to a 2'-F modified sugar is

independently bonded to a 2'-MOE modified sugar. In some embodiments, each natural phosphate linkage bonded to a 2'-F modified sugar is independently bonded to a 2'-MOE modified sugar.

[00566] Among other things, the present disclosure demonstrates that oligonucleotides comprising various blocks and patterns as described herein, e.g., 2'-F blocks, 2'-OMe blocks, 2'-MOE blocks, etc., and/or various internucleotidic linkages and patterns thereof as described herein, can provide improved pharmacodynamics, pharmacokinetics, and/or adenosine editing levels, etc., compared to comparable reference oligonucleotides, e.g., those previously reported in WO 2016/097212, WO 2017/220751, WO 2018/041973, WO 2018/134301A1, WO 2019/158475, WO 2019/219581, WO 2020/157008, WO 2020/165077, WO 2020/201406 or WO 2020/252376. In some embodiments, a reference oligonucleotide is an oligonucleotide reported in WO 2021071858.

[00567] In some embodiments, N_{-2} contains a natural sugar. In some embodiments, sugar of N_{-2} is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00568] In some embodiments, an internucleotidic linkage between N_{-1} and N_{-2} is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001. In some embodiments, N_{-1} is dI, and a linkage between N_{-1} and N_{-2} is a *S*p phosphoryl guanidine internucleotidic linkage. In some embodiments, N_{-1} is dI, and a linkage between N_{-1} and N_{-2} is *S*p n001.

[00569] In some embodiments, N_{-3} contains a natural sugar. In some embodiments, sugar of N_{-3} is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00570] In some embodiments, an internucleotidic linkage between N_{-2} and N_{-3} is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00571] In some embodiments, N_{-4} contains a natural sugar. In some embodiments, sugar of N_{-4} is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00572] In some embodiments, an internucleotidic linkage between N_{-3} and N_{-4} is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00573] In some embodiments, N_{-5} contains a natural sugar. In some embodiments, sugar of N_{-5} is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00574] In some embodiments, an internucleotidic linkage between N_{-4} and N_{-5} is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00575] In some embodiments, N_{-6} contains a natural sugar. In some embodiments, sugar of N_{-6} is a natural DNA sugar. In some embodiments, it is a natural RNA sugar. In some embodiments, it is a modified sugar. In some embodiments, it is a 2'-F modified sugar. In some embodiments, it is a 2'-OR modified sugar, wherein R is C_{1-6} aliphatic as described herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, it is a 2'-OMe modified. In some embodiments, it is a 2'-MOE modified sugar.

[00576] In some embodiments, an internucleotidic linkage between N_{-5} and N_{-6} is a natural phosphate linkage. In some embodiments, it is a modified internucleotidic linkage. In some embodiments, it is a phosphorothioate internucleotidic linkage. In some embodiments, it is a non-negatively charged internucleotidic linkage. In some embodiments, it is a neutral internucleotidic linkage. In some embodiments, it is phosphoryl guanidine internucleotidic linkage. In some embodiments, it is n001. In some embodiments, it is *S*p. In some embodiments, it is *R*p. In some embodiments, it is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p n001. In some embodiments, it is *R*p n001.

[00577] In some embodiments, at least one sugar of N_{-1}, N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a natural DNA sugar. In some embodiments, at least one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-F modified sugar. In some embodiments, at least one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, at least one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-OMe modified sugar. In some embodiments, at least one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-MOE modified sugar. In some embodiments, at least one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a bicyclic sugar, e.g., a LNA sugar, a cEt sugar, etc. In some embodiments, one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-F modified sugar, and each of the other sugars are independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic (e.g., a 2'-OMe modified sugar, a 2'-MOE modified sugar, etc.) or a bicyclic sugar as described herein. In some embodiments, one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-F modified sugar, and each of the other sugars are independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-F modified sugar, and each of the other sugars are independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, one sugar of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is a 2'-F modified sugar, and each of the other sugars are independently a 2'-OMe modified sugar. In some embodiments, sugar of N_{-3} a 2'-F modified sugar. In some embodiments, sugar of N_{-1} is a DNA sugar, sugar of N_{-3} is a 2'-F modified sugar, and sugar of each of N_{-2}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar (e.g., a LNA sugar, an ENA sugar, etc.) as described herein. In some embodiments, sugar of N_{-1} is a DNA sugar, sugar of N_{-3} is a 2'-F modified sugar, and sugar of each of N_{-2}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, sugar of N_{-1} is a DNA sugar, sugar of N_{-3} is a 2'-F modified sugar, and sugar of each of N_{-2}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, sugar of N_{-1} is a DNA sugar, sugar of N_{-3} is a 2'-F modified sugar, and sugar of each of N_{-2}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OMe modified sugar. In some embodiments, N_{-2} forms a 2'-OMe block. In some embodiments, N_{-3} forms a 2'-F block. In some embodiments, N_{-4}, N_{-5}, and N_{-6} forms a 2'-OMe block.

[00578] In some embodiments, at least one of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is bonded to a natural phosphate linkage. In some embodiments, a linkage between N_{-2} and N_{-3} is a natural phosphate linkage. In some embodiments, N_{-2} is bonded to a non-negatively charged internucleotidic linkage. In some embodiments, at least one of N_{-3}, N_{-4}, N_{-5}, and N_{-6} is bonded to a non-negatively charged internucleotidic linkage. In some embodiments, a linkage between N_{-5} and N_{-6} is a non-negatively charged internucleotidic linkage. In some embodiments, at least one of N_{-3}, N_{-4}, N_{-5}, and N_{-6} is bonded to a phosphorothioate internucleotidic linkage. In some embodiments, each of N_{-3}, N_{-4} and N_{-5} is independently bonded to a phosphorothioate internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, it is *R*p. In some embodiments, it is *S*p. In some embodiments, a phosphorothioate internucleotidic linkage is *R*p. In some embodiments, a phosphorothioate internucleotidic linkage is *S*p. In

some embodiments, each phosphorothioate internucleotidic linkage is *S*p. In some embodiments, a linkage between N_{-2} and v-3 is a natural phosphate linkage, a linkage between N_{-3} and N_{-4} is a *S*p phosphorothioate internucleotidic linkage, a linkage between N_{-4} and N_{-5} is a *S*p phosphorothioate internucleotidic linkage, and a linkage between N_{-5} and N_{-6} is a *R*p non-negatively charged internucleotidic linkage (e.g., a *R*p phosphoryl guanidine internucleotidic linkage such as *R*p n001). In some embodiments, a natural phosphate linkage is bonded to at least one modified sugar. In some embodiments, a natural phosphate linkage is bonded to at least one 2'-OR modified sugar wherein R is C_{1-6} aliphatic or a bicyclic sugar. In some embodiments, a natural phosphate linkage is bonded to a 2'-OMe modified sugar. In some embodiments, a natural phosphate linkage is bonded to a 2'-MOE modified sugar. In some embodiments, both sugars bonded to a natural phosphate linkage is independently a modified sugar as described herein.

[00579] In some embodiments, an oligonucleotide comprises a first domain as described herein (e.g., a first domain in which multiple or a majority of or all of sugars are 2'-F modified sugars) and a second domain as described herein (e.g., a second domain in which multiple or a majority of or all of sugars are non-2'-F modified sugars (e.g., 2'-OMe modified sugars)). In some embodiments, a first domain is at the 5' side of a second domain (e.g., various oligonucleotides in (a), Figure 2). In some embodiments, a first domain is at the 3' side of a second domain (e.g., various oligonucleotides in (b), Figure 2). In some embodiments, when a first domain is at the 3' side of a second domain (e.g., various oligonucleotides in (b), Figure 2), there is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more (e.g., 1-20, 2-20, 3-20, 4-20, 5-20, 6-20, 7-20, 7-11, etc.) 5'-side nucleosides of a nucleoside opposite to a target adenosine. In some embodiments, there are at least 3. In some embodiments, there are at least 4. In some embodiments, there are at least 5. In some embodiments, there are at least 6. In some embodiments, there are at least 7. In some embodiments, there are at least 8. In some embodiments, there are at least 9. In some embodiments, there are at least 10. In some embodiments, there are 3. In some embodiments, there are 4. In some embodiments, there are 5. In some embodiments, there are 6. In some embodiments, there are 7. In some embodiments, there are 8. In some embodiments, there are 9. In some embodiments, there are 10. In some embodiments, there are 11. In some embodiments, there are 7-11. In some embodiments, there are 9-11. In some embodiments, there are 10 or 11. In some embodiments, additionally or alternatively, there are at least 15, 16, 17, 18, 19, 20 or more (e.g., 15-30, 16-30, 17-30, 18-30, 18-25, 18-22, etc.) 5'-side nucleosides of a nucleoside opposite to a target adenosine. In some embodiments, there are at least 15. In some embodiments, there are at least 16. In some embodiments, there are at least 17. In some embodiments, there are at least 18. In some embodiments, as described above, there are at least about 5 (e.g., 5-50, 5-40, 5-30, 5-20, 5-10, 5-9, 5, 6, 7, 8, 9, or 10, etc.) 3'-side nucleosides and at least about 15 (e.g., 15-50, 15-40, 15-30, 15-20, 20-30, 20-25, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.) 5'-side nucleosides. In some embodiments, independently about 1-10 (e.g., 2-10, 3-10, 3-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) bicyclic or 2'-OR modified sugars are independently on the 5'-, or 3'-, or both sides of an editing region (e.g., $N_1N_0N_{-1}$), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, independently about 1-10 (e.g., 2-10, 3-10, 3-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-OR modified sugars are independently on the

5'-, or 3'-, or both sides of an editing region, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, independently about 1-10 (e.g., 2-10, 3-10, 3-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) 2'-OMe modified sugars are independently on the 5'-, or 3'-, or both sides of an editing region. In some embodiments, they are on the 5' side. In some embodiments, they are on the 3' sides. In some embodiments, they are on both sides. In some embodiments, it is beneficial that surrounding an editing region, e.g., $N_1N_0N_{-1}$, there are bicyclic or 2'-OR modified sugars, e.g., independently about 1-10 (e.g., 2-10, 3-10, 3-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), on both sides, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, it is beneficial that surrounding an editing region, e.g., $N_1N_0N_{-1}$, there are 2'-OR modified sugars, e.g., independently about 1-10 (e.g., 2-10, 3-10, 3-5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), on both sides, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, on each side there are at least 2. In some embodiments, each 2'-OR modified sugar is a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is a 2'-MOE modified sugar. Certain examples are described in Figure 2 ((a) and/or (b)) and Figure 3.

[00580] One of the many advantages of provided technologies is that much shorter oligonucleotides compared to traditional technologies of others can provide comparable or higher levels of adenosine editing. Those skilled in the art reading the present disclosure will appreciate that longer oligonucleotides (e.g., extending 5' side, 3' side or both sides of a target adenosine) incorporating one or more structural elements (e.g., sugar modifications, nucleobase modifications, internucleotidic linkage modifications, stereochemistry, and/or patterns thereof) of oligonucleotides of the present disclosure (e.g., those described in Figure 2) may also be useful, e.g., for various uses described herein including adenine editing and prevention and/or treatment of conditions, disorders or diseases which can benefit editing of target adenosines.

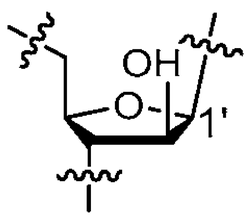
[00581] In some embodiments, ADAR1 p150 may tolerate variations of lengths of 5'-sides and/or 3'-sides and/or positioning of nucleosides opposite to target adenosines more than ADAR1 p110. In some embodiments, the present disclosure provides particularly useful lengths of 5'-sides and/or 3'-sides and/or positioning of nucleosides opposite to target adenosines for editing (e.g., by ADAR1 p110 and/or ADAR1 p150). In some embodiments, certain useful lengths of 5'-sides and/or 3'-sides and/or positioning of nucleosides (e.g., of those oligonucleotides that provide editing, such as WV-12027, WV-42028, WV-42029, WV-42030, WV-42032, and WV-420333; in some embodiments, of WV-42027; in some embodiments, of WV-42028; in some embodiments, of WV-42029; in some embodiments, of WV-42030; in some embodiments, of WV-42031) are useful for editing in cells expressing ADAR1, e.g., ADAR1 p110 and/or p150.

[00582] In some embodiments, each phosphorothioate bonded to a nucleoside opposite to a target adenosine is independently a phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage between N_0 and N_{-1} is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, the internucleotidic linkage between N_{-1} and N_{-2} is a *R*p phosphorothioate internucleotidic linkage.

[00583] In some embodiments, the present disclosure provides oligonucleotides comprising editing regions

that can provide high editing efficiency. In some embodiments, a provided editing region is or comprises 5'-$N_1N_0N_{-1}$–3' as described herein.

[00584] In some embodiments, the present disclosure provides oligonucleotides comprising 5'-$N_1N_0N_{-1}$–3' as described herein.

[00585] In some embodiments, N_0 is as described herein. In some embodiments, N_0 comprises a sugar and a nucleobase as described herein. In some embodiments, N_0 has a natural DNA sugar. In some embodiments, N_0 has a natural RNA sugar. In some embodiments, N_0 has a modified sugar, e.g., a 2'-F modified sugar. In some embodiments, sugar of a nucleobase opposite to a target adenosine, or N_0, is arabinofuranose. In some embodiments, sugar of a nucleobase opposite to a target adenosine, or N_0, is 

, wherein C1' bonds to a nucleobase as described herein. In some embodiments, N_0 has a natural nucleobase. In some embodiments, nucleobase of N_0 is C. In some embodiments, nucleobase of N_0 is b001A. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is cytidine. In some embodiments, N_0 is 2'-F C (wherein 2'-OH of cytidine is replaced with -F). In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, nucleobase of N_0 is not T or U. In some embodiments, nucleobase of N_0 is not T. In some embodiments, nucleobase of N_0 is not U. In some embodiments, N_0 is not a match to A.

[00586] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*.

[00587] In some embodiments, nucleobase of N_1 is T, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is thymidine, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*.

[00588] In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as

deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*.

[00589] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is guanine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyguanosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*. In some embodiments, there are 6 or at least 6 nucleosides to the 3' side of N_0 (e.g., when there are 6, N_{-1} to N_{-6}).

[00590] In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is guanine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyguanosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*. In some embodiments, there are 6 or at least 6 nucleosides to the 3' side of N_0 (e.g., when there are 6, N_{-1} to N_{-6}).

[00591] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_0 is as described herein such as cytosine, b001A, b008U, etc. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*A -3' for editing a target adenosine *A*.

[00592] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F U, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is thymine. In some embodiments, N_1 is 2'-F C, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some

embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-A*A*A -3' for editing a target adenosine *A*.

[00593] In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F A, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F G, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F A, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F A, and N_{-1} is dC. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-A*A*U -3' for editing a target adenosine *A*.

[00594] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F U, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F C, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F C, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-A*A*G -3' for editing a target adenosine *A*.

[00595] In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F G, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F G, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is G,

and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-A*A*C -3' for editing a target adenosine *A*.

[00596] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F U, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-U*A*A -3' for editing a target adenosine *A*.

[00597] In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F U, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-U*A*U -3' for editing a target adenosine *A*.

[00598] In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F U, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F C, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, nucleobase

of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F C, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-U*A*G -3' for editing a target adenosine *A*.

[00599] In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F G, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F U, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F G, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-U*A*C -3' for editing a target adenosine *A*.

[00600] In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F C, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-G*A*A -3' for editing a target adenosine *A*.

[00601] In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F A, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-G*A*U -3' for editing a target adenosine *A*.

[00602] In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F C, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F C, and N_{-1} is dC. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-G*A*G -3' for editing a target adenosine *A*.

[00603] In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is T. In some embodiments, N_1 is 2'-F G, and N_{-1} is dT. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is C. In some embodiments, N_1 is 2'-F G, and N_{-1} is dC. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-G*A*C -3' for editing a target adenosine *A*.

[00604] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and

nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F A, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*U -3' for editing a target adenosine *A*.

[00605] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F U, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F C, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*G -3' for editing a target adenosine *A*.

[00606] In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F A, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F G, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1} is G. In some embodiments, N_1 is 2'-F G, and N_{-1} is dG. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, N_0 is as described herein such as deoxycytidine, b001A, Csm15, b001rA, b008U, etc. In some embodiments, N_0 is deoxycytidine. In some embodiments, N_0 is b001A. In some embodiments, N_0 is Csm15. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-C*A*C -3' for editing a target adenosine *A*.

[00607] In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F U, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F C, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is G, and nucleobase of N_{-1}

$_1$ is A. In some embodiments, N_1 is 2'-F G, and N_{-1} is dA. In some embodiments, nucleobase of N_1 is C, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F C, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is U, and nucleobase of N_{-1} is hypoxanthine. In some embodiments, N_1 is 2'-F U, and N_{-1} is deoxyinosine. In some embodiments, nucleobase of N_1 is A, and nucleobase of N_{-1} is A. In some embodiments, N_1 is 2'-F A, and N_{-1} is dA. In some embodiments, N_0 is b001rA. In some embodiments, N_0 is b008U. In some embodiments, such 5'-$N_1N_0N_{-1}$–3'are particularly useful for targeting RNA comprising 5'-U*A*G -3' for editing a target adenosine *A*.

[00608] In some embodiments, nucleobase U may be replaced with T without lowering editing levels. In some embodiments, nucleobase U may be replaced with T to increase editing levels. In some embodiments, 2'-F U may be replaced with thymidine. See, for example, Figure 19. In some embodiments, N_1 is thymidine. In some embodiments, N_1 is thymidine, N_0 is as described herein, e.g., b001A, b008U, etc. In some embodiments, N_1 is thymidine, N_0 is as described herein, e.g., b001A, b008U, etc., and N_{-1} is I.

[00609] In some embodiments, when being aligned to a target sequence and/or hybridized to a target nucleic acid, N_0 is a wobble or mismatch to A. In some embodiments, N_1 is not a match to its opposite nucleobase. In some embodiments, N_{-1} is not a match to its opposite nucleobase. In some embodiments, two of N_{-1}, N_0 and N_1 are independently not a match to its opposite nucleobase. In some embodiments, N_0 and N_1 are independently not a match to its opposite nucleobase. In some embodiments, N_0 and N_{-1} are independently not a match to its opposite nucleobase. In some embodiments, when it is not a match, it is a wobble. In some embodiments, when it is not a match, it is a mismatch. In some embodiments, nucleobase of N_1 is C and its opposite nucleobase is A. In some embodiments, more nucleosides to the 3' side of N_0 (e.g., 6 or more) may tolerate more mismatches/wobbles of 5'-$N_1N_0N_{-1}$–3'.

[00610] In some embodiments, each internucleotidic linkage bonded to N_0 is independently *S*p phosphorothioate internucleotidic linkages. In some embodiments, each internucleotidic linkage bonded to N_1 is independently *S*p phosphorothioate internucleotidic linkages. In some embodiments, an internucleotidic linkage bonded to N_{-1} is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage bonded to N_{-1} is a neutral internucleotidic linkage. In some embodiments, an internucleotidic linkage bonded to N_{-1} is a phosphoryl guanidine internucleotidic linkage. In some embodiments, an internucleotidic linkage bonded to N_{-1} is n001. In some embodiments, a phosphoryl guanidine internucleotidic linkage, e.g., n001, bonded to N_{-1} (e.g., to its position 3') is chirally controlled and is *R*p. In some embodiments, a phosphoryl guanidine internucleotidic linkage, e.g., n001, bonded to N_{-1} (e.g., to its position 3') is chirally controlled and is *S*p (e.g., in some embodiments, when N_{-1} is dI).

Base Sequences

[00611] As appreciated by those skilled in the art, structural features of the present disclosure, such as nucleobase modification, sugar modifications, internucleotidic linkage modifications, linkage phosphorus stereochemistry, etc., and combinations thereof may be utilized with various suitable base sequences to provide

oligonucleotides and compositions with desired properties and/or activities. For example, oligonucleotides for adenosine modification (e.g., conversion to I in the presence of ADAR proteins) typically have sequences that are sufficiently complementary to sequences of target nucleic acids that comprise target adenosines. Nucleosides opposite to target adenosines can be present at various positions of oligonucleotides. In some embodiments, one or more opposite nucleosides are in first domains. In some embodiments, one or more opposite nucleosides are in second domains. In some embodiments, one or more opposite nucleosides are in first subdomains. In some embodiments, one or more opposite nucleosides are in second subdomains. In some embodiments, one or more opposite nucleosides are in third subdomains. Oligonucleotide of the present disclosure may target one or more target adenosines. In some embodiments, one or more opposite nucleosides are each independently in a portion which has the structure features of a second subdomain, and each independently have one or more or all structural features of opposite nucleosides as described herein. In many embodiments, e.g., for targeting G to A mutations, oligonucleotides may selectively target one and only one target adenosine for modification, e.g., by ADAR to convert into I. In some embodiments, an opposite nucleoside is closer to the 3'-end than to the 5'-end of an oligonucleotide.

[00612] In some embodiments, an oligonucleotide has a base sequence described herein (e.g., in Tables) or a portion thereof (e.g., a span of 10-50, 10-40, 10-30, 10-20, or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or at least 10, at least 15, at least 20, at least 25 contiguous nucleobases) with 0-5 (e.g., 0, 1, 2, 3, 4 or 5) mismatches, wherein each T can be independently substituted with U and vice versa. In some embodiments, an oligonucleotide comprises a base sequence described herein, or a portion thereof, wherein a portion is a span of at least 10 contiguous nucleobases, or a span of at least 15 contiguous nucleobases with 0-5 mismatches. In some embodiments, provided oligonucleotides have a base sequence described herein, or a portion thereof, wherein a portion is a span of at least 10 contiguous nucleobases, or a span of at least 10 contiguous nucleobases with 1-5 mismatches, wherein each T can be independently substituted with U and vice versa.

[00613] In some embodiments, base sequences of oligonucleotides comprise or consist of 10-60 (e.g., about or at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60; in some embodiments, at least 15; in some embodiments, at least 16; in some embodiments, at least 17; in some embodiments, at least 18; in some embodiments, at least 19; in some embodiments, at least 20; in some embodiments, at least 21; in some embodiments, at least 22; in some embodiments, at least 23; in some embodiments, at least 24; in some embodiments, at least 25; in some embodiments, at least 26; in some embodiments, at least 27; in some embodiments, at least 28; in some embodiments, at least 29; in some embodiments, at least 30; in some embodiments, at least 31; in some embodiments, at least 32; in some embodiments, at least 33; in some embodiments, at least 34; in some embodiments, at least 35) bases, optionally contiguous, of a base sequence that is identical or complementary to a base sequence of nucleic acid, e.g., a gene or a transcript (e.g., mRNA) thereof. In some embodiments, the base sequence of an oligonucleotide is or comprises a sequence that is complementary to a target sequence

in a gene or a transcript thereof. In some embodiments, the sequence is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60 or more nucleobases in length.

[00614] In some embodiments, a target sequence is or comprises a characteristic sequence of a nucleic acid sequence (e.g., of an gene or a transcript thereof) in that it defines the nucleic acid sequence over others in a relevant organism; for example, a characteristic sequence is not in or has at least various mismatches from other genomic nucleic acid sequences (e.g., genes) or transcripts thereof in a relevant organism. In some embodiments, a characteristic sequence of a transcript defines that transcript over other transcripts in a relevant organism; for example, in some embodiments, a characteristic sequence is not in transcripts that are transcribed from a different nucleic acid sequence (e.g., a different gene). In some embodiments, transcript variants from a nucleic acid sequence (e.g., mRNA variants of a gene) may share a common characteristic sequence that defines them from, e.g., transcripts of other genes. In some embodiments, a characteristic sequence comprises a target adenosine. In some embodiments, an oligonucleotide selectively forms a duplex with a nucleic acid comprising a target adenosine, wherein the target adenosine is within the duplex region and can be modified by a protein such as ADAR1 or ADAR2.

[00615] Base sequences of provided oligonucleotides, as appreciated by those skilled in the art, typically have sufficient lengths and complementarity to their target nucleic acids, e.g., RNA transcripts (e.g., pre-mRNA, mature mRNA, etc.) for, e.g., site-directed editing of target adenosines. In some embodiments, an oligonucleotide is complementary to a portion of a target RNA sequence comprising a target adenosine (as appreciated by those skilled in the art, in many instances target nucleic acids are longer than oligonucleotides of the present disclosure, and complementarity may be properly assessed based on the shorter of the two, oligonucleotides). In some embodiments, the base sequence of an oligonucleotide has 90% or more identity with the base sequence of an oligonucleotide disclosed in a Table, wherein each T can be independently substituted with U and vice versa. In some embodiments, the base sequence of an oligonucleotide has 95% or more identity with the base sequence of an oligonucleotide disclosed in a Table, wherein each T can be independently substituted with U and vice versa. In some embodiments, the base sequence of an oligonucleotide comprises a continuous span of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 or more bases of an oligonucleotide disclosed in a Table, wherein each T can be independently substituted with U and vice versa, except that one or more bases within the span are abasic (e.g., a nucleobase is absent from a nucleotide).

[00616] In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which comprises the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

[00617] In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which is the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

[00618] In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which comprises at least 15 contiguous bases of the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

[00619] In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which is at least 90% identical to the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

[00620] In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which is at least 95% identical to the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

[00621] In some embodiments, a base sequence of an oligonucleotide is, comprises, or comprises 10-40, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 contiguous bases of the base sequence of any oligonucleotide describer herein, wherein each T may be independently replaced with U and vice versa.

[00622] In some embodiments, an oligonucleotide is an oligonucleotide presented in a Table herein.

[00623] In some embodiments, the base sequence of an oligonucleotide is complementary to that of a target nucleic acid, e.g., a portion comprising a target adenosine.

[00624] In some embodiments, an oligonucleotide has a base sequence which comprises at least 15 contiguous bases (e.g., 15, 16, 17, 18, 19, or 20) of an oligonucleotide in a Table, wherein each T can be independently substituted with U and vice versa.

[00625] In some embodiments, an oligonucleotide comprises a base sequence or portion thereof (*e.g.*, a portion comprising 10-40, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 nucleobases) described in any of the Tables, wherein each T may be independently replaced with U and vice versa, and/or a sugar, nucleobase, and/or internucleotidic linkage modification and/or stereochemistry, and/or a pattern thereof described in any of the Tables, and/or an additional chemical moiety (in addition to an oligonucleotide chain, e.g., a target moiety, a lipid moiety, a carbohydrate moiety, etc.) described in any of the Tables.

[00626] In some embodiments, the terms "complementary," "fully complementary" and "substantially complementary" may be used with respect to the base matching between an oligonucleotide and a target sequence, as will be understood by those skilled in the art from the context of their uses. It is noted that substitution of T for U, or vice versa, generally does not alter the amount of complementarity. As used herein, an oligonucleotide that is "substantially complementary" to a target sequence is largely or mostly complementary but not necessarily 100% complementary. In some embodiments, a sequence (e.g., an oligonucleotide) which is substantially complementary has one or more, e.g., 1, 2, 3, 4 or 5 mismatches when maximally aligned to its target sequence. In some embodiments, an oligonucleotide has a base sequence which is substantially complementary to a target sequence of a target nucleic acid. In some embodiments, an oligonucleotide has a base sequence which is substantially complementary to the complement of the sequence

of an oligonucleotide disclosed herein. As appreciated by those skilled in the art, in some embodiments, sequences of oligonucleotides need not be 100% complementary to their targets for oligonucleotides to perform their functions (e.g., converting A to I in a nucleic acid. In some embodiments, a mismatch is well tolerated at the 5' and/or 3' end or the middle of an oligonucleotide. In some embodiments, one or more mismatches are preferred for adenosine modification as demonstrated herein. In some embodiments, oligonucleotides comprise portions for complementarity to target nucleic acids, and optionally portions that are not primarily for complementarity to target nucleic acids; for example, in some embodiments, oligonucleotides may comprise portions for protein binding. In some embodiments, base sequences of provided oligonucleotides are fully complementary to their target sequences (A-T/U and C-G base pairing). In some embodiments, base sequences of provided oligonucleotides are fully complementary to their target sequences (A-T/U and C-G base pairing) except at a nucleoside opposite to a target nucleoside (e.g., adenosine).

[00627] In some embodiments, the present disclosure provides an oligonucleotide comprising a sequence found in an oligonucleotide described in a Table, wherein one or more U is independently and optionally replaced with T or vice versa. In some embodiments, an oligonucleotide can comprise at least one T and/or at least one U. In some embodiments, the present disclosure provides an oligonucleotide comprising a sequence found in an oligonucleotide described in a Table herein, wherein the said sequence has over 50% identity with the sequence of the oligonucleotide described in a Table. In some embodiments, the present disclosure provides an oligonucleotide whose base sequence is the sequence of an oligonucleotide disclosed in a Table, wherein each T may be independently replaced with U and vice versa. In some embodiments, the present disclosure provides an oligonucleotide comprising a sequence found in an oligonucleotide in a Table, wherein the oligonucleotides have a pattern of backbone linkages, pattern of backbone chiral centers, and/or pattern of backbone phosphorus modifications of the same oligonucleotide or another oligonucleotide in a Table herein.

[00628] In some embodiments, the disclosure provides an oligonucleotide having a base sequence which is, comprises, or comprises a portion of the base sequence of an oligonucleotide disclosed herein, e.g., in a Table, wherein each T may be independently replaced with U and vice versa, wherein the oligonucleotide optionally further comprises a chemical modification, stereochemistry, format, an additional chemical moiety described herein (e.g., a targeting moiety, lipid moiety, carbohydrate moiety, etc.), and/or another structural feature.

[00629] In some embodiments, a "portion" (e.g., of a base sequence or a pattern of modifications or other structural element) is at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 monomeric units long.

[00630] Those skilled in the art reading the present disclosure will appreciate that technologies herein may be utilized to target various target nucleic acids comprising target adenosine for editing. In some embodiments, a target nucleic acid is a transcript of a PiZZ allele. In some embodiments, a target adenosine is …atcgac**A**agaaagggactgaagc... In some embodiments, oligonucleotides of the present disclosure have suitable base sequences so that they have sufficient complementarity to selectively form duplexes with a portion of a transcript that comprise the target adenosine for editing.

[00631] As described herein, nucleosides opposite to target nucleosides (e.g., A) can be positioned at various locations. In some embodiments, an opposite nucleoside is at position 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 3 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 4 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 5 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 6 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 7 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 8 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 9 or more from the 5'-end of an oligonucleotide. In some embodiments, it is at position 10 or more from the 5'-end of an oligonucleotide. In some embodiments, an opposite nucleoside is at position 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 3 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 4 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 5 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 6 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 7 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 8 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 9 or more from the 3'-end of an oligonucleotide. In some embodiments, it is at position 10 or more from the 3'-end of an oligonucleotide. In some embodiments, nucleobases at position 1 from the 5'-end and/or the 3'-end are complementary to corresponding nucleobases in target sequences when aligned for maximum complementarity. In some embodiments, certain positions, e.g., position 6, 7, or 8, may provide higher editing efficiency.

[00632] As examples, certain oligonucleotides comprising certain example base sequences, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties, etc., are presented in Table 1, below. Among other things, these oligonucleotides may be utilized to correct a G to A mutation in a gene or gene product (e.g., by converting A to I). In some embodiments, listed in Tables are stereorandom oligonucleotide compositions. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions.

[00633] In some embodiments, a base sequence is or comprises a particular sequence. In some embodiments, a base sequence is complementary to a base sequence that is or comprises a base sequence that is complementary to a particular sequence. In some embodiments, a base sequence is or comprise a sequence that differs from a particular sequence at no more than 1, 2, 3, 4, or 5 positions. In some embodiments, a base sequence is or comprise a sequence that differs from about 15-30 (e.g., 15-25, 15-20, 20-30, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) consecutive nucleobases of a particular sequence at no more than 1, 2, 3, 4, or 5 positions. In some embodiments, a base sequence is or comprise a sequence that differs from a particular sequence at no more than 1 position. In some embodiments, a base sequence is or comprise a

sequence that differs from a particular sequence at no more than 2 positions. In some embodiments, a base sequence is or comprise a sequence that differs from a particular sequence at no more than 3 positions. In some embodiments, a base sequence is or comprise a sequence that differs from a particular sequence at no more than 4 positions. In some embodiments, a base sequence is or comprise a sequence that differs from a particular sequence at no more than 5 positions. In some embodiments, a particular sequence is or comprises a base sequence selected from Table 1 (e.g., any of Table 1A to Table 1I, 1J to 1O, etc.). In some embodiments, a particular sequence is or comprises 5-30, 10-30, 15-30, 20-30, or 25-30 (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 10 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 11 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 12 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 13 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 14 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 15 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 16 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 17 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 18 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 19 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 20 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 21 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 22 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 23 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 24 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 25 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 26 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 27 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 28 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 29 consecutive bases in a base sequence selected from Table 1. In some embodiments, a particular sequence is or comprises 30 consecutive bases in a base sequence selected from Table 1. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1A. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1B. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1C. In some embodiments, a base sequence selected from

Table 1 is a base sequence selected from Table 1D. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1E. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1F. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1G. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1H. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1I. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1J. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1K. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1L. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1M. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1N. In some embodiments, a base sequence selected from Table 1 is a base sequence selected from Table 1O. In some embodiments, a base sequence is selected from Table 1 (e.g., 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, and/or 1I) of WO 2021/071858, the entirety of which is incorporated herein by reference. In some embodiments, a particular sequence is or comprises UCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises UCCCUUUCTCIUCGA. In some embodiments, a particular sequence is or comprises UCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises UCCCUUUCTCGUCGA. In some embodiments, a particular sequence is or comprises UUCAGUCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises UUCAGUCCCUUUCTCIUCGA. In some embodiments, a particular sequence is or comprises UUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises UUCAGUCCCUUUCTCGUCGA. In some embodiments, a particular sequence is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCIUCGA. In some embodiments, a particular sequence is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA. In some embodiments, a particular sequence is or comprises CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU. In some embodiments, a particular sequence is or comprises ACAUAAUUUACACGAAAGCAAUGCCAUCAC, wherein each U can be independently replaced with T and vice versa. In some embodiments, a particular sequence is or comprises ACAUAAUUUACACGAAAGCAAUGCCAUCAC. In some embodiments, a particular sequence is or comprises AUCCACUGUGGCACCCAGAUUAUCCAUGUU, wherein each U can be independently

replaced with T and vice versa. In some embodiments, a particular sequence is or comprises AUCCACUGUGGCACCCAGAUUAUCCAUGUU. In some embodiments, a particular sequence is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU. In some embodiments, a particular sequence is or comprises CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU.

[00634] Certain oligonucleotides and/or compositions are described in Table 1 below which contains multiple sections, e.g., 1A, 1B, 1C, etc., which may be individually referred to as Table 1A, 1B, 1C, etc. Certain oligonucleotides and/or compositions referred to in the present disclosure are described in WO 2021/071858, e.g., in Table 1 of WO 2021/071858. All oligonucleotides and/or compositions of WO 2021/071858 are incorporated herein by reference.

Table 1. Example oligonucleotides and/or compositions.

Table 1A. Example oligonucleotides and/or compositions that target UGP2.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-40590	fAn001RfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42488	L022*RfAn001RfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	RnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42489	L022*RfA*SfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	RSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42490	fA*SfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	SSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR

Table 1B. Example oligonucleotides and/or compositions that target ACTB.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-39306	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*S5MSfC*Sm5C*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39305	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*Sm5C*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39294	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001R5MRdT*SfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCATCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39293	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001R5MSdT*SfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCATCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39289	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001RT*SfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCATCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR

WV-39267	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*S5MSfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39266	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*S5MRm5dC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39265	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*S5MSm5dC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-39202	L023L010n001RL010n001RL010n001RfAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SmA*SmA*SmG*SmC*SmAn001RmA*SmU*SmG*SfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRnRnRnRSSSSSSSSSSSSSSSnRSSSSSnRSSnR
WV-39203	L023L010n001RL010n001RL010n001RfA*SfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SmA*SmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRnRnRSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-40805	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01n001mU*SmC*SAsm01n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnX
WV-40804	Mod001L001Asm01n001fC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SGsm01n001fA*SAsm01n001mA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01n001mU*SmC*SAsm01n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnXSSSSSSSSSSSSnXSnXSSSSSSSSnXSSnX
WV-40803	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01n001mU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR
WV-40802	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01*n001mU*SmC*SAsm01*n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSn*XSSn*X
WV-40801	Mod001L001Asm01*n001fC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SGsm01*n001fA*SAsm01*n001mA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01*n001mU*SmC*SAsm01*n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	On*XSSSSSSSSSSSSn*XSn*XSSSSSSSSSn*XSSn*X
WV-40800	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAsm01*n001mU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSn*XSSnR

WV-40583	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SA*n001mU*SmC*SmA*n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSSn*XSSn*X
WV-40582	Mod001L001fA*n001fC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*n001fA*SmA*n001mA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SA*n001mU*SmC*SmA*n001mC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	On*XSSSSSSSSSSSSn*XSn*XSSSSSSSSSn*XSSn*X
WV-40581	Mod001L001fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SA*n001mU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	OnRSSSSSSSSSSSSnRSnRSSSSSSSSSn*XSSnR
WV-42331	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfU*SC*STn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGUCTUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42332	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfA*SC*STn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGACTUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42333	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*STn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCTUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42334	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfG*SC*STn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGGCTUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42335	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfU*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGUCAUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42336	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfA*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGACAUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42337	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfG*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGGCAUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42338	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfU*SC*SCn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGUCCUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42339	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfA*SC*SCn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGACCUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR

WV-42340	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SCn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCCUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSSnRSSnR
WV-42341	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfG*SC*SCn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGGCCUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSSnRSSnR
WV-42342	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfU*SC*SIn001SmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGUCIUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSnR
WV-42343	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfA*SC*SIn001SmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGACIUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSnR
WV-42344	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SIn001SmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCIUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSnR
WV-42345	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfG*SC*SIn001SmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGGCIUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSnR
WV-42346	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfU*SC*SGn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGUCGUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42347	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfA*SC*SGn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGACGUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42348	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SGn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCGUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42349	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfG*SC*SGn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGGCGUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-37317	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfGn001RfA*SmAn001RmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSSSSSSSSnRSnRSSSSSSSSnRSSnR
WV-42715	mA*mC*fA*fUfAfAfUfUfUfAfCfAfCfGfAfAmGmGmUmUmCmUmAmAmACCAmU*mC*mC*mU	ACAUAAUUUACACGAAGGUUCUAAACCAUCCU	XXXOOOOOOOOOOOOOOOOOOOOOOXXX

WV-42716	mA*mC*fA*fU*fA*fA*fU*fU*fU*fA*fC*fA*fC*fG*fA*fA*mG*mG*mU*mU*mC*mU*mA*mA*mA*C*C*A*mU*mC*mC*mU	ACAUAAUUUACACGAAGGUUCUAAACCAUCCU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-42717	mA*SmC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SA*SmU*SmC*SmC*SmU	ACAUAAUUUACACGAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42718	mA*SmC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SAn001RmU*SmC*SmCn001RmU	ACAUAAUUUACACGAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42719	mC*mU*mUmUmCmGmUmGmUmAmAmAmUmU*mA*mU*mG*mU	CUUUCGUGUAAAUUAUGU	XXOOOOOOOOOOOXXXX
WV-42720	fC*fU*fUfUfCfGfUfGfUfAfAfAfUfUfA*fU*fG*fU	CUUUCGUGUAAAUUAUGU	XXOOOOOOOOOOOXXXX
WV-42721	mC*mU*mU*mU*mC*mG*mU*mG*mU*mA*mA*mA*mU*mU*mA*mU*mG*mU	CUUUCGUGUAAAUUAUGU	XXXXXXXXXXXXXXXXX
WV-42722	fC*fU*fU*fU*fC*fG*fU*fG*fU*fA*fA*fA*fU*fU*fA*fU*fG*fU	CUUUCGUGUAAAUUAUGU	XXXXXXXXXXXXXXXXX
WV-42723	mC*SmU*SmU*SmU*SmC*SmG*SmU*SmG*SmU*SmA*SmA*SmA*SmU*SmU*SmA*SmU*SmG*SmU	CUUUCGUGUAAAUUAUGU	SSSSSSSSSSSSSSSSS
WV-42724	fC*SfU*SfU*SfU*SfC*SfG*SfU*SfG*SfU*SfA*SfA*SfA*SfU*SfU*SfA*SfU*SfG*SfU	CUUUCGUGUAAAUUAUGU	SSSSSSSSSSSSSSSSS
WV-42725	mU*mU*mCmGmUmGmUmAmAmAmUmUmA*mU*mG*mU	UUCGUGUAAAUUAUGU	XXOOOOOOOOOOXXXX
WV-42726	fU*fU*fCfGfUfGfUfAfAfAfUfUfA*fU*fG*fU	UUCGUGUAAAUUAUGU	XXOOOOOOOOOOXXXX
WV-42727	mU*mU*mC*mG*mU*mG*mU*mA*mA*mA*mU*mU*mA*mU*mG*mU	UUCGUGUAAAUUAUGU	XXXXXXXXXXXXXXXX
WV-42728	fU*fU*fC*fG*fU*fG*fU*fA*fA*fA*fU*fU*fA*fU*fG*fU	UUCGUGUAAAUUAUGU	XXXXXXXXXXXXXXXX
WV-42729	mU*SmU*SmC*SmG*SmU*SmG*SmU*SmA*SmA*SmA*SmU*SmU*SmA*SmU*SmG*SmU	UUCGUGUAAAUUAUGU	SSSSSSSSSSSSSSS
WV-42730	fU*SfU*SfC*SfG*SfU*SfG*SfU*SfA*SfA*SfA*SfU*SfU*SfA*SfU*SfG*SfU	UUCGUGUAAAUUAUGU	SSSSSSSSSSSSSSS

WV-42738	fC*fU*fCfCfUfCfUfUfCfUfCfGfAfCfAmAmAmGmGmUmUmCmUmAmAmACCAmU*mC*mC*mU	CUCCUCUUCUCGACAAAGGUUCUAAACCAUCCU	XXOOOOOOOOOOOOOOOOOOOOOOOOOOXXX
WV-42739	fC*fU*fC*fC*fU*fC*fU*fU*fC*fU*fC*fG*fA*fC*fA*mA*mA*mG*mG*mU*mU*mC*mU*mA*mA*mA*C*C*A*mU*mC*mC*mU	CUCCUCUUCUCGACAAAGGUUCUAAACCAUCCU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-42740	fC*SfU*SfC*SfC*SfU*SfC*SfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfA*SmA*SmA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SA*SmU*SmC*SmC*SmU	CUCCUCUUCUCGACAAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42741	fC*SfU*SfC*SfC*SfU*SfC*SfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfA*SmA*SmA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SAn001RmU*SmC*SmCn001RmU	CUCCUCUUCUCGACAAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42746	fC*fU*fCfCfUfCfUfUfCfUfCfGfAfCfAmGmGmUmUmCmUmAmAmACCAmU*mC*mC*mU	CUCCUCUUCUCGACAGGUUCUAAACCAUCCU	XXOOOOOOOOOOOOOOOOOOOOOOOOOOXXX
WV-42747	fC*fU*fC*fC*fU*fC*fU*fU*fC*fU*fC*fG*fA*fC*fA*mG*mG*mU*mU*mC*mU*mA*mA*mA*C*C*A*mU*mC*mC*mU	CUCCUCUUCUCGACAGGUUCUAAACCAUCCU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-42748	fC*SfU*SfC*SfC*SfU*SfC*SfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SA*SmU*SmC*SmC*SmU	CUCCUCUUCUCGACAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42749	fC*SfU*SfC*SfC*SfU*SfC*SfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SAn001RmU*SmC*SmCn001RmU	CUCCUCUUCUCGACAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42731	fU*fG*fUfCfGfAfGfAfAfGfAfGfGfAfGfAmAmCmAmAmUmAmUmGmCmUmAmAfAfUfGfUfU*fG*fU*fU	UGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUU	XXOOOOOOOOOOOOOOOOOOOOOOOOOOXXX
WV-42732	fU*fG*fU*fC*fG*fA*fG*fA*fA*fG*fA*fG*fG*fA*fG*fA*mA*mC*mA*mA*mU*mA*mU*mG*mC*mU*mA*mA*fA*fU*fG*fU*fU*fG*fU*fU	UGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-42733	fU*SfG*SfU*SfC*SfG*SfA*SfG*SfA*SfA*SfG*SfA*SfG*SfG*SfA*SfG*SfA*SmA*SmC*SmA*SmA*SmU*SmA*SmU*SmG*SmC*SmU*SmA*SmA*SfA*SfU*SfG*SfU*SfU*SfG*SfU*SfU	UGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS

Table 1C. Example oligonucleotides and/or compositions that target LUC.

ID	Description	Base Sequence	Stereochemistry/ Linkage

WV-42707	mA*mC*mA*fUfAfAfUfUfUfAfCfAfCfGfAfAfAfGmAmAmGmGmUmUmCmUmAmAmACCAmU*mC*mC*mU	ACAUAAUUUACACGAAAGAAGGUUCUAAACCAUCCU	XXXOOOOOOOOOOOOOOOOOOOOOOOOOXXX
WV-42708	mA*mC*mA*fU*fA*fA*fU*fU*fU*fA*fC*fA*fC*fG*fA*fA*fA*fG*mA*mA*mG*mG*mU*mU*mC*mU*mA*mA*mA*C*C*A*mU*mC*mC*mU	ACAUAAUUUACACGAAAGAAGGUUCUAAACCAUCCU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-42709	mA*SmC*SmA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SmA*SmA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SA*SmU*SmC*SmC*SmU	ACAUAAUUUACACGAAAGAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
WV-42710	mA*SmC*SmA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SmA*SmA*SmG*SmG*SmU*SmU*SmC*SmU*SmA*SmA*SmA*SC*SC*SAn001RmU*SmC*SmCn001RmU	ACAUAAUUUACACGAAAGAAGGUUCUAAACCAUCCU	SSSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1D. Example oligonucleotides and/or compositions that target SERPINA1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-42060	mCn001RmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfCn001RfA	CAGCUUCAGUCCCUUUCUCIUCGAUGGUCA	nRSSSSSSSSSSSSSSSSSSnSSSSSSSSSnR
WV-42059	mGn001RmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfUn001RfC	GCAGCUUCAGUCCCUUUCUCIUCGAUGGUC	nRSSSSSSSSSSSSSSSSSSSnSSSSSSSSnR
WV-42058	mAn001RmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfGn001RfU	AGCAGCUUCAGUCCCUUUCUCIUCGAUGGU	nRSSSSSSSSSSSSSSSSSSSSnSSSSSSSnR
WV-42057	mCn001RmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfGn001RfG	CAGCAGCUUCAGUCCCUUUCUCIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42056	mCn001RmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfUn001RfG	CCAGCAGCUUCAGUCCCUUUCUCIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42055	mCn001RmC*SmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SmU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfAn001RfU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42054	mCn001RmC*SmC*SmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SmG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfGn001RfA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSnR

WV-42053	mGn001RmC*SmC*SmC*SmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SmA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfCn001RfG	GCCCCAGCAGCUUCAGUCCCUUUCUCIUCG	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-42052	mGn001RmG*SmC*SmC*SmC*SmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SmC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfUn001RfC	GGCCCCAGCAGCUUCAGUCCCUUUCUCIUC	nRSSSSSSSSSSSSSSSSSSSSSSSSnSnR
WV-42051	mUn001RmG*SmG*SmC*SmC*SmC*SmC*SmA*SmG*SmC*SmA*SmG*SmC*SmU*SmU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU	UGGCCCCAGCAGCUUCAGUCCCUUUCUCIU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnS
WV-42050	fUn001RC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmA*SmU*SmG*SmC*SmA*SmCn001RmG	UCIUCGAUGGUCAGCACAGCCUUAUGCACG	nRSnSSSSSSSSSSSSSSSSSSSSSSSnR
WV-42049	fCn001RfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmA*SmU*SmG*SmC*SmAn001RmC	CUCIUCGAUGGUCAGCACAGCCUUAUGCAC	nRSSnSSSSSSSSSSSSSSSSSSSSSnR
WV-42048	fUn001RfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmA*SmU*SmG*SmCn001RmA	UCUCIUCGAUGGUCAGCACAGCCUUAUGCA	nRSSSnSSSSSSSSSSSSSSSSSSSSSnR
WV-42047	fUn001RfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmA*SmU*SmGn001RmC	UUCUCIUCGAUGGUCAGCACAGCCUUAUGC	nRSSSSnSSSSSSSSSSSSSSSSSSSSnR
WV-42046	fUn001RfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmA*SmUn001RmG	UUUCUCIUCGAUGGUCAGCACAGCCUUAUG	nRSSSSSnSSSSSSSSSSSSSSSSSSSnR
WV-42045	fCn001RfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmU*SmAn001RmU	CUUUCUCIUCGAUGGUCAGCACAGCCUUAU	nRSSSSSSnSSSSSSSSSSSSSSSSSSnR
WV-42044	fCn001RfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmU*SmUn001RmA	CCUUUCUCIUCGAUGGUCAGCACAGCCUUA	nRSSSSSSSnSSSSSSSSSSSSSSSSSnR
WV-42043	fCn001RfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmC*SmUn001RmU	CCCUUUCUCIUCGAUGGUCAGCACAGCCUU	nRSSSSSSSSnSSSSSSSSSSSSSSSSSnR
WV-42042	fUn001RfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmC*SmCn001RmU	UCCCUUUCUCIUCGAUGGUCAGCACAGCCU	nRSSSSSSSSSnSSSSSSSSSSSSSSSSnR

WV-42041	fGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SfG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmG*SmCn001RmC	GUCCCUUUCUCIUCGAUGGUCAGCACAGCC	nRSSSSSSSSSSnSSSSSSSSSSSSSSSSnR
WV-42040	fAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SfC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmA*SmGn001RmC	AGUCCCUUUCUCIUCGAUGGUCAGCACAGC	nRSSSSSSSSSSSnSSSSSSSSSSSSSSSnR
WV-42039	fCn001RfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SfU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmC*SmAn001RmG	CAGUCCCUUUCUCIUCGAUGGUCAGCACAG	nRSSSSSSSSSSSSnSSSSSSSSSSSSSSnR
WV-42038	fUn001RfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmA*SmCn001RmA	UCAGUCCCUUUCUCIUCGAUGGUCAGCACA	nRSSSSSSSSSSSSSnSSSSSSSSSSSSSSnR
WV-42037	fUn001RfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmC*SmAn001RmC	UUCAGUCCCUUUCUCIUCGAUGGUCAGCAC	nRSSSSSSSSSSSSSSnSSSSSSSSSSSSSSnR
WV-42036	fCn001RfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmCn001RmA	CUUCAGUCCCUUUCUCIUCGAUGGUCAGCA	nRSSSSSSSSSSSSSSSnSSSSSSSSSSSSSnR
WV-42035	fGn001RfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmGn001RmC	GCUUCAGUCCCUUUCUCIUCGAUGGUCAGC	nRSSSSSSSSSSSSSSSSnSSSSSSSSSSSSnR
WV-42034	fAn001RfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmAn001RmG	AGCUUCAGUCCCUUUCUCIUCGAUGGUCAG	nRSSSSSSSSSSSSSSSSSnSSSSSSSSSSSnR
WV-42033	fCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmCn001RmA	CAGCUUCAGUCCCUUUCUCIUCGAUGGUCA	nRSSSSSSSSSSSSSSSSSSnSSSSSSSSSSnR
WV-42032	fGn001RfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmUn001RmC	GCAGCUUCAGUCCCUUUCUCIUCGAUGGUC	nRSSSSSSSSSSSSSSSSSSSnSSSSSSSSnR
WV-42031	fAn001RfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmGn001RmU	AGCAGCUUCAGUCCCUUUCUCIUCGAUGGU	nRSSSSSSSSSSSSSSSSSSSSnSSSSSSSnR
WV-42030	fCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmGn001RmG	CAGCAGCUUCAGUCCCUUUCUCIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSnSSSSSSnR

WV-42029	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCAGCAGCUUCAGUCCCUUUCUCIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42027	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42026	fGn001RfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmCn001RmG	GCCCCAGCAGCUUCAGUCCCUUUCUCIUCG	nRSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-42025	fGn001RfG*SfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmUn001RmC	GGCCCCAGCAGCUUCAGUCCCUUUCUCIUC	nRSSSSSSSSSSSSSSSSSSSSSnSnR
WV-42024	fUn001RfG*SfG*SfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU	UGGCCCCAGCAGCUUCAGUCCCUUUCUCIU	nRSSSSSSSSSSSSSSSSSSSSSSSnS
WV-42076	mCn001RfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfU*SfA*SfU*SfG*SfC*SfAn001RfC	CUCIUCGAUGGUCAGCACAGCCUUAUGCAC	nRSSnSSSSSSSSSSSSSSSSSSSSnR
WV-42075	mUn001RmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfU*SfA*SfU*SfG*SfCn001RfA	UCUCIUCGAUGGUCAGCACAGCCUUAUGCA	nRSSSnSSSSSSSSSSSSSSSSSSSnR
WV-42074	mUn001RmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfU*SfA*SfU*SfGn001RfC	UUCUCIUCGAUGGUCAGCACAGCCUUAUGC	nRSSSSnSSSSSSSSSSSSSSSSSSnR
WV-42073	mUn001RmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfU*SfA*SfUn001RfG	UUUCUCIUCGAUGGUCAGCACAGCCUUAUG	nRSSSSSnSSSSSSSSSSSSSSSSSSnR
WV-42072	mCn001RmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfU*SfAn001RfU	CUUUCUCIUCGAUGGUCAGCACAGCCUUAU	nRSSSSSSnSSSSSSSSSSSSSSSSSnR
WV-42071	mCn001RmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfU*SfUn001RfA	CCUUUCUCIUCGAUGGUCAGCACAGCCUUA	nRSSSSSSSnSSSSSSSSSSSSSSSSSnR

WV-42070	mCn001RmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfC*SfUn001RfU	CCCUUUCUCIUCGAUGGUCAGCACAGCCUU	nRSSSSSSSSnSSSSSSSSSSSSSSSSnR
WV-42069	mUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfC*SfCn001RfU	UCCCUUUCUCIUCGAUGGUCAGCACAGCCU	nRSSSSSSSSSnSSSSSSSSSSSSSSSnR
WV-42068	mGn001RmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfG*SfCn001RfC	GUCCCUUUCUCIUCGAUGGUCAGCACAGCC	nRSSSSSSSSSSnSSSSSSSSSSSSSSnR
WV-42067	mAn001RmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfC*SfA*SfGn001RfC	AGUCCCUUUCUCIUCGAUGGUCAGCACAGC	nRSSSSSSSSSSSnSSSSSSSSSSSSSSnR
WV-42065	mUn001RmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfA*SfCn001RfA	UCAGUCCCUUUCUCIUCGAUGGUCAGCACA	nRSSSSSSSSSSSSSnSSSSSSSSSSSSSnR
WV-42064	mUn001RmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfC*SfAn001RfC	UUCAGUCCCUUUCUCIUCGAUGGUCAGCAC	nRSSSSSSSSSSSSSnSSSSSSSSSSSSSnR
WV-42063	mCn001RmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfG*SfCn001RfA	CUUCAGUCCCUUUCUCIUCGAUGGUCAGCA	nRSSSSSSSSSSSSSSnSSSSSSSSSSSSnR
WV-42062	mGn001RmC*SmU*SmU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SfU*SfC*SfG*SfA*SfU*SfG*SfG*SfU*SfC*SfA*SfGn001RfC	GCUUCAGUCCCUUUCUCIUCGAUGGUCAGC	nRSSSSSSSSSSSSSSSnSSSSSSSSSSSnR
WV-42688	fCn001RfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmG*SmCn001RmA	CUUCAGUCCCUUUCUAIUCGAUGGUCAGCA	nRSSSSSSSSSSSSSSSnSSSSSSSSSSnR
WV-42687	fGn001RfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmA*SmGn001RmC	GCUUCAGUCCCUUUCUAIUCGAUGGUCAGC	nRSSSSSSSSSSSSSSSnSSSSSSSSSSnR
WV-42686	fAn001RfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmC*SmAn001RmG	AGCUUCAGUCCCUUUCUAIUCGAUGGUCAG	nRSSSSSSSSSSSSSSSSSnSSSSSSSSSnR
WV-42685	fCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmU*SmCn001RmA	CAGCUUCAGUCCCUUUCUAIUCGAUGGUCA	nRSSSSSSSSSSSSSSSSSSnSSSSSSSSSnR

WV-42684	fGn001RfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmG*SmUn001RmC	GCAGCUUCAGUCCCUUUCUAIUCGAUGGUC	nRSSSSSSSSSSSSSSSSSSnSSSSSSSnR
WV-42683	fAn001RfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmG*SmGn001RmU	AGCAGCUUCAGUCCCUUUCUAIUCGAUGGU	nRSSSSSSSSSSSSSSSSSSSnSSSSSSSnR
WV-42682	fCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmGn001RmG	CAGCAGCUUCAGUCCCUUUCUAIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42681	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCAGCAGCUUCAGUCCCUUUCUAIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42679	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42678	fGn001RfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmCn001RmG	GCCCCAGCAGCUUCAGUCCCUUUCUAIUCG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-42677	fGn001RfG*SfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmUn001RmC	GGCCCCAGCAGCUUCAGUCCCUUUCUAIUC	nRSSSSSSSSSSSSSSSSSSSSSSSnSnR
WV-42676	fUn001RfG*SfG*SfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SmC*SmA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU	UGGCCCCAGCAGCUUCAGUCCCUUUCUAIU	nRSSSSSSSSSSSSSSSSSSSSSSSSnS
WV-42327	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnXSSnR
WV-38630	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb001A*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnXSSnR
WV-38629	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*SrC*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnXSSnR

WV-42328	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUIUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR
WV-38923	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*Gn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUGUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSXnXSSnR
WV-38622	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb001A*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTAIUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR
WV-38621	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*SrC*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTCIUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR
WV-38620	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*SC*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTCIUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR
WV-42600	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTAIUCGA	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSnR
WV-42960	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SmCn001RmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSSnR
WV-42962	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSSnR
WV-42958	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SmCn001RmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSnRSnRSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42328	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SmUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUIUCGA	nRSSSSSSSSSSSSnRSnRSSSSSSSSnXSSnR

WV-42327	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*SIn001mU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnXSSnR
WV-42939	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SrCsm14*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42938	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001rA*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42937	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm17*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42936	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm16*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSXnSSSSnR
WV-42935	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm15*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSXnSSSSnR
WV-42933	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb007C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42932	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb004C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42030	fCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmU*SmGn001RmG	CAGCAGCUUCAGUCCCUUUCUCIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42029	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCAGCAGCUUCAGUCCCUUUCUCIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR

WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42027	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42682	fCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmGn001RmG	CAGCAGCUUCAGUCCCUUUCUAIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42681	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCAGCAGCUUCAGUCCCUUUCUAIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42679	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43117	mCn001RmC*SmCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43116	fCn001RfC*SfCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43115	fCn001RfC*SfCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43113	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43112	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42986	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmCn001RmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnRSnR
WV-42985	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmUn001RmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSnRSSnR
WV-42984	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001An001RIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnRnSSSSnR
WV-42983	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfUn001Rb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnRSnSSSSnR
WV-42982	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmCn001RfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnRSSnSSSSnR
WV-42981	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmUn001RmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnSSSSnR
WV-42980	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmUn001RmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSSnSSSSnR
WV-42979	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmUn001RmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSSSnSSSSnR
WV-42978	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmCn001RmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSSSnSSSSnR
WV-42977	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmCn001RmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSSSnSSSSnR
WV-42976	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmCn001RmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSSSnSSSSnR

WV-42975	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfUn001RmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42974	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42973	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfAn001RfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42972	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfCn001RfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42971	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42970	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfUn001RfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42969	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfCn001RfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42968	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfGn001RfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSnRSSSSSSSSSSnSSSSnR
WV-42967	fCn001RfC*SfC*SfA*SfG*SfC*SfAn001RfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSnRSSSSSSSSSSnSSSSnR
WV-42966	fCn001RfC*SfC*SfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSnRSSSSSSSSSSnSSSSnR
WV-42965	fCn001RfC*SfC*SfA*SfGn001RfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSnRSSSSSSSSSSnSSSSnR
WV-42964	fCn001RfC*SfC*SfAn001RfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSnRSSSSSSSSSSnSSSSnR

WV-42963	fCn001RfC*SfCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSnRSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43081	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*RmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSRSnR
WV-43080	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*RmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSRSnR
WV-43078	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Rb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSRSnSSSSnR
WV-43077	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*RfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSRSSnSSSSnR
WV-43076	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*RmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSnSSSSnR
WV-43075	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*RmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSSnSSSSnR
WV-43074	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*RmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSSSnSSSSnR
WV-43073	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*RmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSSSnSSSSnR
WV-43072	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*RmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSSSnSSSSnR
WV-43071	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*RmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSRSSSSSnSSSSnR

WV-43070	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*RmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43069	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*RfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43068	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*RfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43067	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*RfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43066	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*RfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43065	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*RfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43064	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*RfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSRSSSSSSSSSSnSSSSnR
WV-43063	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*RfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSRSSSSSSSSSSnSSSSnR
WV-43062	fCn001RfC*SfC*SfA*SfG*SfC*SfA*RfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSRSSSSSSSSSSnSSSSnR
WV-43061	fCn001RfC*SfC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSSSSSSSnSSSSnR
WV-43060	fCn001RfC*SfC*SfA*SfG*RfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSRSSSSSSSSSSnSSSSnR
WV-43059	fCn001RfC*SfC*SfA*RfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSRSSSSSSSSSSnSSSSnR

WV-43058	fCn001RfC*SfC*RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSRSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43022	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RfU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43021	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43020	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43019	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43018	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SfU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43017	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SfC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43016	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43015	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SfU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43014	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SfU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43013	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SfC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-43012	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43011	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43037	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43036	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SmG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43035	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SmA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43034	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SmC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43033	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SmU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43032	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SmU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43031	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SmC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43030	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SmG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43029	fCn001RfC*SfC*SfA*SfG*SfC*SmA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-43028	fCn001RfC*SfC*SfA*SfG*SmC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43027	fCn001RfC*SfC*SfA*SmG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43026	fCn001RfC*SfC*SmA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43025	fCn001RfC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43024	fCn001RmC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43023	mCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43057	fCn001RfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43056	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43055	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmCn001RmG	CCCAGCAGCUUCAGUCCCUUUCUAIUCG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-43054	fCn001RfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43053	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR

WV-43052	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43051	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43050	fGn001RfC*SfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SmG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	GCCCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43049	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmUn001RmG	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43048	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmA*SmU*SmGn001RmG	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAUGG	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43047	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmCmCn001RmCmUn001RmUmUn001RmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSOnROnROnRSSSnSSSSnR
WV-43046	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmUmUn001RmUmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSOnROSSSnSSSSnR
WV-43045	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmCmCn001RmUmUn001RmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSOnROnRSSSnSSSSnR
WV-43044	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmCmUn001RmUmUn001RmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSOnROnRSSSnSSSSnR
WV-43043	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmUmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSOSSSnSSSSnR
WV-43042	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmUmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSOSSSSnSSSSnR

WV-43041	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmUmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSOSSSSSnSSSSnR
WV-43040	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmCmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSOSSSSSnSSSSnR
WV-43039	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmCmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSOSSSSSSSnSSSSnR
WV-43038	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmCmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSOSSSSSSSnSSSSnR
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43118	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43119	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43120	Mod001L001mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43121	Mod001L001fCn001RfC*SfCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43122	Mod001L001fCn001RfC*SfCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43123	Mod001L001mCn001RmC*SmCn001RfA*SfG*SfCn001RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfGn001RfU*SfCn001RfC*SfC*SfU*SfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSnRSSnRSSSSSSSnRSnRSSSnRSSSSnSSSSnR
WV-43745	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSnSSSnR

WV-43746	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43747	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUUIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43748	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCGUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43749	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*SC*SIn001SmU*SfC*SfGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43750	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SfC*SfGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43751	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb008U*SIn001SmU*SfC*SfGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUUIUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43752	Mod001L001fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfC*SC*SGn001RmU*SfC*SfGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCGUCGA	OnRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43753	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*SC*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43118	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43754	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb008U*SIn001SmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43755	Mod001L001fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfC*SC*SGn001RmU*SmC*SfG*SfAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCGUCGAU	OnRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-43698	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*SC*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGCGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

WV-43697	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43696	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*SC*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCACGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43695	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43694	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-43693	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-43692	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCACIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-42027	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-43691	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*SC*SCn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGCCUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43690	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*SCn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCCUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43689	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*SC*SCn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCACCUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43688	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SCn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCCUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43687	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*SC*SAn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGCAUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

WV-43686	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*SAn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCAUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43685	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*SC*SAn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCACAUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43683	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*SC*STn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGCTUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43682	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*SC*STn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCCTUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43681	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*SC*STn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCACTUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43680	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*STn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUCTUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43725	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb001A*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCGAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43724	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb001A*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43722	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43721	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCGAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43720	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43719	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR

WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43705	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb001A*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGAGUCGA	nRSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43704	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb001A*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCAGUCGA	nRSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43703	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb001A*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCAAGUCGA	nRSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43702	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAGUCGA	nRSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43699	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCAAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSnR
WV-42679	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43733	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb008U*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCGUGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-43732	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb008U*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-43731	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb008U*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAUGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-43730	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SGn001RmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-43729	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb008U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCGUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-43728	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb008U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCUUUCCUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43727	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb008U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCUUUCAUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43726	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43713	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb008U*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGUGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43712	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb008U*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCUGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43711	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb008U*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCAUGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43710	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SGn001RmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUUGUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-43709	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfG*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCGUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43708	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfC*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCCUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43707	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfA*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCAUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43706	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42679	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR

WV-43714	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43706	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43715	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*ST*Sb008U*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCTUIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-42679	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SmU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43718	fCn001RfC*SfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SmC*SfU*Sb001A*SIn001SmU*SfC*SfGn001RmA	CCCCAGCAGCUUCAGUCCCUUUCUAIUCGA	nRSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44275	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44274	mCn001RmC*SmC*SfA*SfG*SfC*SmA*SfG*SfC*SmU*SfUn001RmC*SfA*SfGn001RfU*SmC*SfC*SfC*SfUn001RfU*SmU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSSSnRSSSSSnSSSSnR
WV-44273	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSnROSnROSSSSOSSSnSOSSnR
WV-44272	mCn001RmC*SmC*SfA*SfG*SfC*SmA*SfG*SfC*SmU*SfUn001RmC*SfA*SfGn001RfU*SmC*SfC*SfC*SfU*SfU*SmU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSnSSSSnR
WV-44271	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfU*SmCfA*SfG*SfUmC*SfC*SfC*SfU*SfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSSOSSOSSSSSOSSSnSOSSnR
WV-44270	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfU*SmCfA*SfG*SfU*SmCfC*SfC*SfU*SfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSSOSSSOSSSSOSSSnSOSSnR
WV-44269	mCn001RmC*SmC*SfA*SfG*SfC*SmA*SfG*SfC*SmU*SfU*SmC*SfA*SfG*SfU*SmC*SfC*SfC*SfU*SfU*SmU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-44226	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SmU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44227	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfCfCn001RfUfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSOnROnRSSSnSSSSnR
WV-44191	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSOnRSOSSSOSSSSnSOSSnR
WV-44190	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44189	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSOnRSOSSSSSSSnSOSSnR
WV-44187	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSSnRSSSSSSSSSnSOSSnR
WV-44186	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSSnRSSSSSSSSSnSSSSnR
WV-44184	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfGfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSnROSSSSSSSSSnSOSSnR
WV-44183	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSnRSSSSSSSSSnSOSSnR
WV-44182	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSnRSSSSSSSSSnSSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44224	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*RfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSSnRSSRSSSSSSSnSSSSnR

WV-44223	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSSnRSSSSSSSSSSnSRSSnR
WV-44222	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSSnSRSSnR
WV-44219	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSnRSSSSSSSSSSnSRSSnR
WV-44218	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSnRSSSSSSSSSSnSRSSnR
WV-44217	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSnRSSSSSSSSSSnSSSSnR
WV-44216	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*RfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSSSSSSSRSSSSSSnSSSSnR
WV-44215	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSSSSSSSSSSSSSSnSRSSnR
WV-44214	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*RfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSRSSnR
WV-44213	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSSSSSSSSSSSSSSnSSSSnR
WV-44199	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SI*RmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSRSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44200	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmA*SmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSS

WV-44198	mC*SmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	SSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44203	mCn001RmC*SmC*SmA*SmG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44202	mCn001RmC*SmC*SmA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44201	mCn001RmC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44225	mCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44268	Cn001RC*SC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44267	mCn001RmC*SC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44266	mCn001RC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44265	Cn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-44264	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSnR

WV-44179	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SCsm15*In001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSOSSSSnRSOnRSSSSSSSSSXnSOSSnR
WV-44178	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001rA*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSOnRSSSSSSSSSSnSOSSnR
WV-44188	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSSSnRSOnRSSSSSSSSSSnSOSSnR
WV-44210	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001rA*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSSnSSSSnR
WV-44185	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSSnSSSSnR
WV-44175	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001rA*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44209	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfU*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUUAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44208	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfU*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGUUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44207	mCn001RmC*SmC*SfA*SfG*SfU*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGUAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44206	mCn001RmC*SmU*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCUAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44205	mCn001RmU*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CUCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-44204	mUn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SteoRmU	UCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-43114	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44464	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44465	Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR

Table 1E. Example oligonucleotides and/or compositions that target SERPINA1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-42680	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44285	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm01n001b001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnXSnSSSSnR
WV-44286	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SGsm01n001mU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnXSSSnR
WV-44287	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm01n013b001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSOSnSSSSnR
WV-44288	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001A*SGsm01n013mU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSSSOSSSnR
WV-44327	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm18n001b001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnXSnSSSSnR
WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

WV-44278	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm01n001C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSnXSnSSSSnR
WV-44279	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm01n001In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnXnSSSSnR
WV-44280	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*STsm01n001In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUTIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnXnSSSSnR
WV-44281	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SGsm01n001mU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnXSSSnR
WV-44282	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm01n013C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSOSnSSSSnR
WV-44283	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm01n013In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSOnSSSSnR
WV-44284	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SGsm01n013mU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSOSSSnR
WV-44328	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*STsm18n001C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSnXSnSSSSnR

Table 1F. Example oligonucleotides and/or compositions that target SERPINA1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-44275	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44464	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44466	L001mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR

WV-44515	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46313	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-46314	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-46315	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmC*SfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSSnRSOnROOSSSOSSSSnSOSSnR
WV-46316	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-46317	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSSnROSnROSSSnROOSSSnSOSSnR
WV-44464	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-46406	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROSSSSOOSSSnSOSSnR
WV-46407	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-46408	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46409	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46410	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SmUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR

WV-46411	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46412	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SmUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46413	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SfUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46414	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46415	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46468	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*SfU*Sb008U*SIn001SrUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46469	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*SfU*Sb008U*SIn001SUsm15fC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-46470	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*SfU*Sb008U*SIn001SrUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-44464	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	OnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44487	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-44482	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47029	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnSOSSnR

WV-47030	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RfCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47031	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47032	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SmUn001RfUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47033	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SmUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47034	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RfCfA*SfGn001RfUmC*SfC*SfC*SmUn001RfUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47035	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SfGn001RfUmC*SfC*SfC*SmUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47036	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47037	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47038	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47039	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SmGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47040	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RfCfA*SmGn001RfUmC*SfC*SfC*SmUn001RfUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47041	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SmGn001RfUmC*SfC*SfC*SmUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR

WV-47042	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*STeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47141	mU*fG*mUmUmAfAmAmCmAmUmGmCmCfUmAfAmAmCmGmCmU*mU*mU	UGUUAAACAUGCCUAAACGCUUU	XXOOOOOOOOOOOOOOOOOXX
WV-47142	Mod001L001mA*mGmCmGmUmUfUmAfGfGfCmAmUmGmUmUmUmAmAmC*mA	AGCGUUUAGGCAUGUUUAACA	OXOOOOOOOOOOOOOOOOOX
WV-47143	L001mA*mGmCmGmUmUfUmAfGfGfCmAmUmGmUmUmUmAmAmC*mA	AGCGUUUAGGCAUGUUUAACA	OXOOOOOOOOOOOOOOOOOX
WV-47339	mCn051RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47340	mCn057RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47341	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn051RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47342	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn057RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47343	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*SC*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47344	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*SC*Sb008U*SGn001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUGUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47345	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb012U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47346	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb013U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47347	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-47348	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb002A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47349	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb003A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47350	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb004I*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTIIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47351	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb002G*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTGIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47352	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb009U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47353	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb001A*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47354	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb002A*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47355	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb003A*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47356	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb008U*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47357	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb001C*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47358	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb008C*b008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSXSnSOSSnR
WV-47359	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*STsm11*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-47360	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*STsm12*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47361	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb004C*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47362	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb007C*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47363	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*SCsm17*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47364	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47365	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb001A*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCACIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47366	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb002A*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCACIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47367	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb003A*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCACIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47368	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb008U*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47369	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb001C*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47370	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb008C*C*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSXSnSOSSnR
WV-47371	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*STsm11*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-47372	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*STsm12*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47373	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb004C*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47374	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*Sb007C*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47375	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*SCsm17*SC*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46461	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47376	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SI*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47377	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb001An001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUAUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47378	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb002An001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUAUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47379	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb003A*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUAUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47380	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb008Un001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUUUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47381	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb001Cn001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnROSSnR
WV-47382	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb008Cn001mUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnXOSSnR

WV-47383	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*STsm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUTUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47384	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*STsm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUTUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47385	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb004C*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47386	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb007C*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47387	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SCsm17*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47388	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SIn001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnROSSnR
WV-47389	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SI*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47390	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb001An001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCAUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnROSSnR
WV-47391	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb002An001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCAUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnROSSnR
WV-47392	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb003A*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCAUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47393	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb008Un001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCUUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnROSSnR
WV-47394	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb001Cn001RmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSnROSSnR

WV-47395	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb008Cn001mUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnXOSSnR
WV-47396	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*STsm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCTUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47397	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*STsm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCTUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47398	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb004C*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47399	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb007C*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47400	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SCsm17*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47401	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SCsm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47402	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SCsm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47403	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb009Csm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47404	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb009Csm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47405	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SCsm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR
WV-47406	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*SCsm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSSOSSnR

WV-47407	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb009Csm11*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSSOSSnR
WV-47408	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*SC*Sb009Csm12*SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCCUCGAU	nRSSSSOSSOSnROSnROSSSOOSSSSOSSnR
WV-47483	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb002G*In001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTGIUCGAU	nRSSSSOSSOSnROSnROSSSOOSSXnSOSSnR
WV-46313	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47595	L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47596	L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47597	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47598	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SfUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-47599	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-47600	Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-47601	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RmCfA*SfGn001RfUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSOnROSnROSSOnROOSSSnSOSSnR
WV-47602	Mod001L001m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAT	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-47603	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47604	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47605	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomAfG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47606	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47607	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47608	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47609	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*STeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-46407	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47610	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47611	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SmUn001RfCfA*SmGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47612	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47613	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUTTCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR

WV-47614	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47615	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUTTCTUIUCGAT	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47616	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47617	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUTTCTUIUCGAU	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47618	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47619	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUTTCTUIUCGAT	nRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-46452	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47620	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47621	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47622	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46453	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47623	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-47624	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47625	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46457	mCn001RmC*SmC*SfA*SfG*Sm5CeomAfG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47626	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomAfG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47627	mCn001RmC*SmC*SfA*SfG*Sm5CeomAfG*SfC*STeofUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47628	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomAfG*SfC*STeofUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47629	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmU*STeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47630	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmU*STeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47631	m5Ceon001Rm5Ceo*Sm5Ceo*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmU*STeofC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAT	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-47641	Mod012L030*mCmCmCfAfGmCfAfGfCfUfUfCfAfGfUfCfCfCfUmUfUfCfUb001AImUfCmGmAmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	XOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
WV-47642	Mod012L030*mC*mC*mC*fA*fG*mC*fA*fG*fC*fU*fU*fC*fA*fG*fU*fC*fC*fC*fU*mU*fU*fC*fU*b001A*I*mU*fC*mG*mA*mU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	XXXXXXXXXXXXXXXXXXXXXXXXXXXXX
WV-47643	Mod012L030*mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	XnRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-47644	Mod012L030*mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb00	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	XnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

	8U*SIn001SmUfC*SmG*SmAn001RmU		
WV-47645	Mod012L030*mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	XnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-47646	Mod012L030*mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	XnRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-47647	Mod012L030*mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	XnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-47648	Mod012L030*mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUUTCTUIUCGAU	XnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-48453	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	OnRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-48454	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUm5CeomC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	OnRSSSSOSSOSnROSnROOSSSOOSSSnSOSSnR
WV-48455	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn003SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-48456	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn004SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-48457	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn008SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-48458	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn025SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-48459	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn026SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-49085	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR

	Sb008U*SIn001SmUfC*SmG*SmAn001RmU		
WV-49086	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUm5Ceo*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-49087	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-49088	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-49089	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*Sm5CeoTeo*SmUn001Rm5CeofA*SfGn001RmUm5Ceom5Ceo*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-49090	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*SmUmUn001RmCfA*SfGn001RfUm5Ceo*SfC*SmCmUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSOnROOSSSSnSOSSnR
WV-49092	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUm5Ceo*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSSnSOSSnR
WV-49093	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCTeo*SfUn001RmCfA*SfGn001RfUm5Ceo*SfC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-47606	Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSSnSOSSnR
WV-46460	mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-49094	L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCTUCAGUCCCUTTCTUIUCGAU	OnRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-49095	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*Sb014In001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-49096	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb014I*SIn001Sm	CCCAGCAGCUUCAGUCCCUUUCTIIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

	UfC*SmG*SmAn001RmU		
WV-44230	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb010U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44231	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb001C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44232	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SL034*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44233	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb008C*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44234	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb011U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44235	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb002G*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUGIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44236	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*Sb012U*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44237	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SUsm04*C*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44238	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SCsm04*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44239	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SUsm04*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44240	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SUsm04*Csm04*In001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44241	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SUsm04*Usm04*I	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

	n001SmU*SmC*SmG*SmAn001RmU		
WV-42934	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SrCsm13*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44242	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb008U*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44243	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb010U*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44244	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb001C*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44362	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb008C*b001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSXSnSSSSnR
WV-44246	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb011U*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44247	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*Sb012U*Sb001A*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44248	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb008U*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44249	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb010U*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44250	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb001C*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44363	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb008C*b001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSXSnSSSSnR
WV-44251	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb008C*Sb001A*SIn0	CCCAGCAGCUUCAGUCCCUUUCCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

	01SmU*SfC*SmG*SmAn001RmU		
WV-44252	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb011U*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44253	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*Sb012U*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44377	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*STsm11*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44378	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SCsm11*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44379	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SGsm11*SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSnR
WV-44380	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*STsm11*SCsm11*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44381	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*STsm12*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44382	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SCsm12*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44383	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SGsm12*SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAGUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSnR
WV-44384	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*STsm12*SCsm12*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44385	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb009Csm11*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44386	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb009Csm12*SIn	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR

	001SmU*SfC*SmG*SmAn001RmU		
WV-44387	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SL010*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCAIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44388	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SL010*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44389	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SL010n001RmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44390	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SC*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44276	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfAfGn001RfUmC*SfC*SfC*SfUn001RfUmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOSnROOnROSSSnROOSSSnSOSSnR
WV-44277	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmUfUn001RmCfAfGn001RfUmCfC*SfC*SfUn001RfUmUfC*SfU*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSOSSOOnROOnROOSSnROOSSSnSOSSnR
WV-42028	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44349	fCn002RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44350	fCn006RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44351	fCn020RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn001SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44352	fCn001RfC*SfC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SmC*SmC*SmC*SmU*SmU*SmU*SmC*SfU*SC*SIn006SmU*SmC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-46312	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb00	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

	8U*SIn001SmUfC*SmG*SmAn001RmU		
WV-46318	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-46319	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSOSnROSnROSSOnROOSSSnSOSSnR
WV-46320	Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-46321	Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SmCfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSOSnRSOSSSnSOSSnR
WV-46322	Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmCfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOOSSSnRSOnROOOSSOSSSSnSOSSn
WV-46323	Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSSOSSSnSOSSnR

Table 1G. Example oligonucleotides and/or compositions that target KEAP1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-47580	fGn001RfG*SfU*SfG*SfA*SfC*SfA*SfG*SfC*SfC*SfA*SfC*SfG*SfC*SfC*SmC*SmA*SmC*SmC*SmC*SmC*SmA*SC*Sb008U*SCn001RmC*SfG*SmG*SmCn001RmC	GGUGACAGCCACGCCCACCCCACUCCGGCC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47567	fCn001RfU*SfG*SfU*SfC*SfC*SfA*SfG*SfG*SfA*SfA*SfC*SfG*SfU*SfG*SmU*SmG*SmA*SmC*SmC*SmA*SmU*SmC*SA*Sb008U*SAn001RmG*SfC*SmCn001RmU	CUGUCCAGGAACGUGUGACCAUCAUAGCCU	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47579	fUn001RfG*SfU*SfC*SfC*SfA*SfG*SfG*SfA*SfA*SfC*SfG*SfU*SfG*SfU*SmG*SmA*SmC*SmC*SmA*SmU*SmC*SA*Sb008U*SAn001RmG*SfC*SmC*SmUn001RmC	UGUCCAGGAACGUGUGACCAUCAUAGCCUC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47565	fCn001RfU*SfG*SfU*SfU*SfC*SfA*SfG*SfC*SfU*SfG*SfG*SfU*SfC*SfC*SmU*SmG*SmA*SmC*SmC*SmA*SmU*SmC*SA*Sb008U*SAn001RmG*SfC*SmCn001RmC	CUGUUCAGCUGGUCCUGACCAUCAUAGCCC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47577	fUn001RfG*SfU*SfU*SfC*SfA*SfG*SfC*SfU*SfG*SfG*SfU*SfC*SfC*SfU*SmG*SmA*SmC*SmC*SmA*SmU*SmC*SA*Sb008U*SAn	UGUUCAGCUGGUCCUGACCAUCAUAGCCCC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

	001RmG*SfC*SmC*SmCn001RmC		
WV-47576	fCn001RfA*SfG*SfG*SfA*SfC*SfG*SfC*SfA*SfG*SfA*SfC*SfG*SfC*SfC*SmU*SmG*SmC*SmC*SmC*SmC*SmG*SC*Sb008U*STn001RmC*SfG*SmG*SmAn001RmU	CAGGACGCAGACGCCUGCCCCGCUTCGGAU	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47575	fCn001RfA*SfU*SfA*SfC*SfC*SfU*SfC*SfU*SfC*SfC*SfA*SfC*SfA*SfC*SmU*SmG*SmU*SmU*SmG*SmU*SmG*SG*Sb008U*SIn001SmG*SfA*SmU*SmGn001RmC	CAUACCUCUCCACACUGUUGUGGUIGAUGC	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-47570	fAn001RfC*SfU*SfC*SfA*SfC*SfC*SfU*SfC*SfU*SfC*SfC*SfA*SfC*SfA*SmC*SmU*SmG*SmU*SmU*SmG*SmU*SmG*SG*Sb008U*SIn001SmG*SfA*SmUn001RmG	ACUCACCUCUCCACACUGUUGUGGUIGAUG	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-47562	fGn001RfA*SfG*SfU*SfC*SfG*SfG*SfU*SfG*SfU*SfU*SfG*SfC*SfC*SfG*SmU*SmC*SmG*SmG*SmG*SmC*SmG*SmA*SG*Sb008U*STn001RmG*SfU*SmUn001RmC	GAGUCGGUGUUGCCGUCGGGCGAGUTGUUC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47561	fAn001RfG*SfU*SfC*SfG*SfG*SfU*SfG*SfU*SfU*SfG*SfC*SfC*SfG*SfU*SmC*SmG*SmG*SmG*SmC*SmG*SmA*SmG*ST*Sb008U*SIn001SmU*SfU*SmCn001RmC	AGUCGGUGUUGCCGUCGGGCGAGTUIUUCC	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-47574	fAn001RfG*SfU*SfC*SfG*SfG*SfU*SfG*SfU*SfU*SfG*SfC*SfC*SfG*SfU*SmC*SmG*SmG*SmG*SmC*SmG*SmA*SG*Sb008U*STn001RmG*SfU*SmU*SmCn001RmC	AGUCGGUGUUGCCGUCGGGCGAGUTGUUCC	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47573	fGn001RfU*SfC*SfG*SfG*SfU*SfG*SfU*SfU*SfG*SfC*SfC*SfG*SfU*SfC*SmG*SmG*SmG*SmC*SmG*SmA*SmG*ST*Sb008U*SIn001SmU*SfU*SmC*SmCn001RmU	GUCGGUGUUGCCGUCGGGCGAGTUIUUCCU	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-47560	fUn001RfG*SfU*SfU*SfG*SfC*SfC*SfG*SfU*SfC*SfG*SfG*SfG*SfC*SfG*SmA*SmG*SmU*SmU*SmG*SmU*SmU*SmC*SC*Sb008U*SIn001SmC*SfC*SmGn001RmC	UGUUGCCGUCGGGCGAGUUGUUCCUICCGC	nRSSSSSSSSSSSSSSSSSSSSSSSSnSSSnR
WV-47559	fAn001RfG*SfG*SfU*SfA*SfG*SfC*SfU*SfG*SfA*SfG*SfC*SfG*SfA*SfC*SmU*SmG*SmU*SmC*SmG*SmG*SmA*SmA*SG*Sb008U*SAn001RmG*SfC*SmCn001RmG	AGGUAGCUGAGCGACUGUCGGAAGUAGCCG	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1H. Example oligonucleotides and/or compositions that target NRF2.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-47558	fGn001RfG*SfG*SfC*SfU*SfG*SfG*SfC*SfU*SfG*SfA*SfA*SfU*SfU*SfG*SmG*SmG*SmA*SmG*SmA*SmA*SmA*ST*Sb008U*SCn001RmA*SfC*SmC*SmUn001RmG	GGGCUGGCUGAAUUGGGAGAAATUCACCUG	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47548	fGn001RfC*SfU*SfG*SfA*SfA*SfU*SfU*SfG*SfG*SfG*SfA*SfG*SfA*SfA*SmA*SmU*SmU*SmC*SmA*SmC*SmC*SmU*SG*Sb008U	GCUGAAUUGGGAGAAAUUCACCUGUCUCUU	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR

	*SCn001RmU*SfC*SmUn001RmU		
WV-47547	fUn001RfG*SfA*SfA*SfU*SfU*SfG*SfG*SfG*SfA*SfG*SfA*SfA*SfA*SfU*SmU*SmC*SmA*SmC*SmC*SmU*SmG*SmU*SC*Sb008U*SCn001RmU*SfU*SmCn001RmA	UGAAUUGGGAGAAAUUCACCUGUCUCUUCA	nRSSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47556	fGn001RfA*SfA*SfU*SfU*SfG*SfG*SfG*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SmC*SmA*SmC*SmC*SmU*SmG*SmU*SC*Sb008U*SCn001RmU*SfU*SmC*SmAn001RmU	GAAUUGGGAGAAAUUCACCUGUCUCUUCAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47546	fAn001RfU*SfU*SfG*SfG*SfG*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfC*SfA*SmC*SmC*SmU*SmG*SmU*SmC*SmU*SmC*ST*Sb008U*SCn001RmA*SfU*SmCn001RmU	AUUGGGAGAAAUUCACCUGUCUCTUCAUCU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47554	fGn001RfG*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfC*SfA*SfC*SfC*SfU*SfG*SmU*SmC*SmU*SmC*SmU*SmU*SmC*SA*Sb008U*SCn001RmU*SfA*SmG*SmUn001RmU	GGAGAAAUUCACCUGUCUCUUCAUCUAGUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47545	fGn001RfG*SfG*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfC*SfA*SfC*SfC*SfU*SmG*SmU*SmC*SmU*SmC*SmU*SmU*SmC*SA*Sb008U*SCn001RmU*SfA*SmGn001RmU	GGGAGAAAUUCACCUGUCUCUUCAUCUAGU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47553	fAn001RfU*SfA*SfC*SfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfU*SfU*SfA*SmC*SmU*SmC*SmC*SmA*SmA*SmG*SA*Sb008U*SCn001RmU*SfA*SmU*SmAn001RmU	AUACUUCUCGACUUACUCCAAGAUCUAUAU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47543	fCn001RfU*SfU*SfC*SfU*SfC*SfG*SfA*SfC*SfU*SfU*SfA*SfC*SfU*SfC*SmC*SmA*SmA*SmG*SmA*SmU*SmC*SmU*SA*Sb008U*SAn001RmU*SfC*SmUn001RmU	CUUCUCGACUUACUCCAAGAUCUAUAUCUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47551	fCn001RfU*SfC*SfG*SfA*SfC*SfU*SfU*SfA*SfC*SfU*SfC*SfC*SfA*SfA*SmG*SmA*SmU*SmC*SmU*SmA*SmU*SA*Sb008U*SCn001RmU*SfU*SmG*SmCn001RmC	CUCGACUUACUCCAAGAUCUAUAUCUUGCC	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47542	fUn001RfC*SfU*SfC*SfG*SfA*SfC*SfU*SfU*SfA*SfC*SfU*SfC*SfC*SfA*SmA*SmG*SmA*SmU*SmC*SmU*SmA*SmU*SA*Sb008U*SCn001RmU*SfU*SmGn001RmC	UCUCGACUUACUCCAAGAUCUAUAUCUUGC	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47550	fGn001RfA*SfC*SfU*SfU*SfA*SfC*SfU*SfC*SfC*SfA*SfA*SfG*SfA*SfU*SmC*SmU*SmA*SmU*SmA*SmU*SmC*ST*Sb008U*SGn001RmC*SfC*SmU*SmCn001RmC	GACUUACUCCAAGAUCUAUAUCTUGCCUCC	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47541	fCn001RfG*SfA*SfC*SfU*SfU*SfA*SfC*SfU*SfC*SfC*SfA*SfA*SfG*SfA*SmU*SmC*SmU*SmA*SmU*SmA*SmU*SmC*ST*Sb008U*SGn001RmC*SfC*SmUn001RmC	CGACUUACUCCAAGAUCUAUAUCTUGCCUC	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1I. Example oligonucleotides and/or compositions that target UGP2.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-48161	Mod001L001mAn001RmU*SmC*SfC*SfA*SfC*SmUfG*SfU*SfG*SfG*SfCn001RfA*SfCfCn001RfC*SfA*SfG*SfA*SfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSSOSSSSnRSOnRSSSSSOSSSSnROSnR
WV-48162	Mod001L001mAn001RmU*SmC*SfC*SfA*SfC*SfUmG*SfU*SfGmG*SfCn001RmAfC*SfCn001RfCmA*SfG*SfA*SfUn001RfU*SmAfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSSOSSOSnROSnROSSnRSOSSSnROSnR
WV-48164	Mod001L001mAn001RmU*SmC*SfC*SfA*SmCmU*SfG*SfUmG*SfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfA*SmUmUfA*SfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSOSSOSnROSnROSSSSOOSSSSnROSnR
WV-47046	mAn001RmU*SmC*SfC*SfA*SfC*SmUfG*SfU*SfG*SfG*SfCn001RfA*SfCfCn001RfC*SfA*SfG*SfA*SfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSOSSSSnRSOnRSSSSSOSSSSnROSnR
WV-47053	mAn001RmU*SmC*SfC*SfA*SmCmUfG*SfU*SmGfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfAn001RmUmUfA*SfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOOSSOnROSnROSSSnROOSSSSnROSnR
WV-47049	mAn001RmU*SmC*SfC*SfA*SfCmU*SfG*SfUmG*SfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfAn001RfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOSSOSnROSnROSSSnRSOSSSSnROSnR
WV-47044	mAn001RmU*SmC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*SC*SAn001RmU*SfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47043	fAn001RfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SmC*SmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47044	mAn001RmU*SmC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*SC*SAn001RmU*SfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47045	mAn001RmU*SmC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47046	mAn001RmU*SmC*SfC*SfA*SfC*SmUfG*SfU*SfG*SfG*SfCn001RfA*SfCfCn001RfC*SfA*SfG*SfA*SfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSOSSSSnRSOnRSSSSSOSSSSnROSnR

WV-47047	mAn001RmU*SmC*SfC*SfA*SfC*SfUmG*SfU*SfGmG*SfCn001RmAfC*SfCn001RfCmA*SfG*SfA*SfUn001RfU*SmAfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSOSSOSnROSnROSSSnRSOSSSnROSnR
WV-47048	mAn001RmU*SmC*SfC*SfA*SmCfU*SfG*SfU*SfG*SfGn001RfC*SfAfCn001RfC*SfC*SfA*SfG*SfA*SmUfU*SfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOSSSSnRSOnRSSSSSOSSSSSnROSnR
WV-47049	mAn001RmU*SmC*SfC*SfA*SfCmU*SfG*SfUmG*SfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfAn001RfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOSSOSnROSnROSSSnRSOSSSSnROSnR
WV-47050	mAn001RmU*SmC*SfC*SfA*SfC*SmUmG*SfU*SfGmG*SfCn001RmAfC*SfCn001RfCmA*SfG*SfA*SfU*SmUmAfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSOSSOSnROSnROSSSSOOSSSnROSnR
WV-47051	mAn001RmU*SmC*SfC*SfA*SfC*SmUmGfU*SfG*SmGfCn001RmAfC*SfCn001RfCmA*SfG*SfA*SfUn001RmUmAfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSSOOSSOnROSnROSSSnROOSSSnROSnR
WV-47052	mAn001RmU*SmC*SfC*SfA*SmCmU*SfG*SfUmG*SfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfA*SmUmUfA*SfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOSSOSnROSnROSSSOOSSSSnROSnR
WV-47053	mAn001RmU*SmC*SfC*SfA*SmCmUfG*SfU*SmGfGn001RmCfA*SfCn001RfCmC*SfA*SfG*SfAn001RmUmUfA*SfU*SC*SC*SAn001RmUfG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	nRSSSSOOSSOnROSnROSSSnROOSSSSnROSnR
WV-44560	fUn001RfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCCAUGUUA	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44561	mUn001RmC*SmC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*SC*SAn001RmU*SfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCCAUGUUA	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44562	mUn001RmC*SmC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*Sb008U*SAn001RmU*SfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCUAUGUUA	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44562	mUn001RmC*SmC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfC*SfC*SfC*SfC*SfA*SfG*SfA*SfU*SfU*SfA*SfU*SfC*Sb008U*SAn001RmU*SfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCUAUGUUA	nRSSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44563	mUn001RmC*SmC*SfA*SfC*SmUfG*SfU*SfG*SfG*SfCn001RfA*SfCfCn001RfC*SfA*SfG*SfA*SfU*SmUfA*SfU*SfC*SC*SAn001RmUfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCCAUGUUA	nRSSSSOSSSSnRSOnRSSSSSOSSSSnROSSnR

WV-44564	mUn001RmC*SmC*SfA*SfC*SfUmG*SfU*SfGmG*SfCn001RmAfC*SfCn001RfCmA*SfG*SfA*SfUn001RfU*SmAfU*SfC*Sb008U*SAn001RmUfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCUAUGUUA	nRSSSSOSSOSnROSnROSSSnRSOSSSnROSSnR
WV-44565	mUn001RmC*SmC*SfA*SfC*SfUmG*SfU*SfGmG*SfC*SmAfC*SfC*SfC*SmAfG*SfA*SfU*SfU*SmAfU*SfC*Sb008U*SAn001RmUfG*SmU*SmUn001RmA	UCCACUGUGGCACCCAGAUUAUCUAUGUUA	nRSSSSOSSOSSOSSSOSSSSOSSnROSSnR

Table 1J. Example oligonucleotides and/or compositions that target ACTB.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-47054	fAn001RfC*SfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SmA*SmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47055	mAn001RmC*SmA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SfC*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmU*SfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47056	mAn001RmC*SmA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SfC*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmU*SmC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47057	mAn001RmC*SmA*SfU*SfA*SfA*SmUfU*SfU*SfA*SfC*SfAn001RfC*SfGfAn001RfA*SfA*SfG*SfC*SfA*SmAfU*SfG*SfC*SC*SAn001RmUfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSOSSSSnRSOnRSSSSSOSSSSnROSnR
WV-47058	mAn001RmC*SmA*SfU*SfA*SfA*SfUmU*SfU*SfAmC*SfAn001RmCfG*SfAn001RfAmA*SfG*SfC*SfAn001RfA*SmUfG*SfC*SC*SAn001RmUfC*SmAn001RmC	ACAUAAUUUACACGAAAGCAAUGCCAUCAC	nRSSSSSOSSOSnROSnROSSSnRSOSSSnROSnR
WV-44554	fCn001RfA*SfU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SmA*SmG*SmC*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmU*SmC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCCAUCACC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44555	mCn001RmA*SmU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SfC*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmU*SfC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCCAUCACC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44556	mCn001RmA*SmU*SfA*SfA*SfU*SfU*SfU*SfA*SfC*SfA*SfC*SfG*SfA*SfA*SfA*SfG*SfC*SfA*SfA*SfU*SfG*SfC*Sb008U*SAn001RmU*SfC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCUAUCACC	nRSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44557	mCn001RmA*SmU*SfA*SfA*SmUfU*SfU*SfA*SfC*SfAn001RfC*SfGfAn001RfA*SfA*SfG*SfC*SfA*SmAfU*SfG*SfC*SC*SAn001RmUfC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCCAUCACC	nRSSSSOSSSSnRSOnRSSSSSOSSSSnROSSnR

WV-44558	mCn001RmA*SmU*SfA*SfA*SfUmU*SfU*SfAmC*SfAn001RmCfG*SfAn001RfAmA*SfG*SfC*SfAn001RfA*SmUfG*SfC*SC*SAn001RmUfC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCCAUCACC	nRSSSSOSSOSnROSnROSSSnRSOSSSnROSSnR
WV-44559	mCn001RmA*SmU*SfA*SfA*SfUmU*SfU*SfAmC*SfA*SmCfG*SfA*SfA*SmAfG*SfC*SfA*SfA*SmUfG*SfC*SC*SAn001RmUfC*SmA*SmCn001RmC	CAUAAUUUACACGAAAGCAAUGCCAUCACC	nRSSSSOSSOSSOSSSOSSSSOSSnROSSnR

Table 1K. Example oligonucleotides and/or compositions that target EEEF.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-47059	fCn001RfC*SfA*SfA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SmC*SmA*SmC*SmA*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmC*SmU*SmGn001RmU	CCAACCAGAAAUUGGCACAAAUGCCACUGU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47060	mCn001RmC*SmA*SfA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SfC*SfA*SfC*SfA*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmC*SfU*SmGn001RmU	CCAACCAGAAAUUGGCACAAAUGCCACUGU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-47061	mCn001RmC*SmA*SfA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SfC*SfA*SfC*SfA*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmC*SmU*SmGn001RmU	CCAACCAGAAAUUGGCACAAAUGCCACUGU	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1L. Example oligonucleotides and/or compositions that target SRSF.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-44551	fUn001RfA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SmG*SmA*SmU*SmA*SmU*SmG*SmU*SfC*SC*SAn001RmC*SmA*SmG*SmAn001RmA	UAAUCCAUCUCUUCAGAUAUGUCCACAGAA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44552	mUn001RmA*SmA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*SC*SAn001RmC*SfA*SmG*SmAn001RmA	UAAUCCAUCUCUUCAGAUAUGUCCACAGAA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-44553	mUn001RmA*SmA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*Sb008U*SAn001RmC*SfA*SmG*SmAn001RmA	UAAUCCAUCUCUUCAGAUAUGUCUACAGAA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47062	fUn001RfU*SfA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SmA*SmG*SmA*SmU*SmA*SmU*SmG*SmU*SfC*SC*SAn001RmC*SmA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCCACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR
WV-47063	mUn001RmU*SmA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*SC*SAn001RmC*SfA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCCACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSnRSSSnR

WV-47064	mUn001RmU*SmA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*SC*SAn001RmC*SmA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCCACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-48183	mUn001RmU*SmA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*Sb001A*SAn001RmC*SfA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCAACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-48184	mUn001RmU*SmA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SfC*Sb008U*SAn001RmC*SfA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCUACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-48185	mUn001RmU*SmA*SfA*SfU*SfC*SfC*SfA*SfU*SfC*SfU*SfC*SfU*SfU*SfC*SfA*SfG*SfA*SfU*SfA*SfU*SfG*SfU*SC*SC*SAn001RmC*SfA*SmGn001RmA	UUAAUCCAUCUCUUCAGAUAUGUCCACAGA	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1M. Example oligonucleotides and/or compositions that target EEF1A1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-44548	fCn001RfA*SfA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SfC*SmA*SmC*SmA*SmA*SmA*SmU*SmG*SfC*SC*SAn001RmC*SmU*SmG*SmUn001RmG	CAACCAGAAAUUGGCACAAAUGCCACUGUG	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-44549	mCn001RmA*SmA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SfC*SfA*SfC*SfA*SfA*SfA*SfU*SfG*SfC*SC*SAn001RmC*SfU*SmG*SmUn001RmG	CAACCAGAAAUUGGCACAAAUGCCACUGUG	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR
WV-44550	mCn001RmA*SmA*SfC*SfC*SfA*SfG*SfA*SfA*SfA*SfU*SfU*SfG*SfG*SfC*SfA*SfC*SfA*SfA*SfA*SfU*SfG*SfC*Sb008U*SAn001RmC*SfU*SmG*SmUn001RmG	CAACCAGAAAUUGGCACAAAUGCUACUGUG	nRSSSSSSSSSSSSSSSSSSSSSSSSSnRSSnR

Table 1N. Example oligonucleotides and/or compositions that target UGP2.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-44002	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmAmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSOSSSSSSSnRSSnR
WV-44003	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmAmG*SmAmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSOSOSSSSSnRSSnR
WV-44004	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmAmG*SmAmU*SmUmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSOSOSSSSnRSSnR

WV-44005	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmAmG*SmAmU*SmUmA*SmUfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSOSOSOSSnRSSnR
WV-44006	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmC*SmA*SmGmA*SmUmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnRSSSOSOSSSSSnRSSnR
WV-44007	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmC*SmA*SmGmA*SmUmU*SmAmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnRSSSOSOSOSSSnRSSnR
WV-44008	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmA*SmGmA*SmUmU*SmA*SmUfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSSOSOSSOSSnRSSnR
WV-44009	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmC*SmA*SmGmA*SmUmU*SmAmUfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROSSOSOSOOSSnRSSnR
WV-44012	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfCmCmAmGmAmUmUmAmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnRSSSSSSSnROOOOOOOSSSnRSSnR
WV-44060	Mod001L001fA*SfU*SfCn001RfC*SfA*SfCn001RfUfGfUfGfGfCfAfCn001RfCmCmAmGmAmUmUmAmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OSSnRSSnROOOOOOOnROOOOOOOOSSSnRSSnR
WV-43980	Mod001L001fAn001RfU*SfC*SfC*SfA*SfC*SfU*SfG*SfU*SfG*SfG*SfC*SfA*SfCn001RfC*SmCmAmGmAmUmUmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSSSSSSSSSnRSOOOOOOSSSSnRSSnR
WV-43983	Mod001L001fAn001RfU*SfC*SfC*SfAfC*SfU*SfG*SfU*SfGfG*SfC*SfA*SfCn001RfC*SmCn001RmA*SmGmA*SmU*SmU*SmAmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSOSSSSOSSSnRSnRSOSSSOSSSnRSSnR
WV-43984	Mod001L001fAn001RfU*SfC*SfC*SfA*SfC*SmU*SfG*SfU*SmG*SfG*SmC*SmA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSSSSSSSSSnRSnRSSSSSSSSSnRSSnR
WV-43985	Mod001L001fAn001RfU*SfC*SfC*SfA*SfCn001RmU*SfG*SfU*SmGfG*SmCmA*SfCn001RfC*SmCn001RmA*SmG*SmA*SmU*SmU*SmA*SmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSnRSSSOSOSnRSnRSSSSSSSSSnRSSnR
WV-43986	Mod001L001fAn001RfU*SfC*SfC*SfA*SfCn001RmU*SfG*SfU*SmGfG*SmCmA*SfCn001RfC*SmCn001RmA*SmG*SmAmU*SmU*SmAmU*SfC*SC*SAn001RmU*SmG*SmUn001RmU	AUCCACUGUGGCACCCAGAUUAUCCAUGUU	OnRSSSSnRSSSOSOSnRSnRSSOSSOSSSnRSSnR

Table 1O. Example oligonucleotides and/or compositions that target SERPINA1.

ID	Description	Base Sequence	Stereochemistry/ Linkage
WV-47595	L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	OnRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-44176	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SCsm15*In001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSXnSSSSnR
WV-44177	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfU*SfC*SfA*SfG*SfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb008U*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSSSSSSSSSSSSSSSnSSSSnR
WV-44180	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOnRSSSSSSSSSnSOSSnR
WV-44211	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*SCsm15*In001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSXnSSSSnR
WV-44212	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb008U*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSSSSSSnRSSnRSSSSSSSSSnSSSSnR
WV-43144	mU*fA*mAmGmGfGmAmGmGmAmAmAmUfAmUfAmGmAmGmGmG*mU*mU	UAAGGGAGGAAAUAUAGAGGGUU	XXOOOOOOOOOOOOOOOOOXX
WV-44192	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmC*SfC*SfU*SfU*SfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOnRSOSSSSSSSSnSOSSnR
WV-44193	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44194	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmC*SfC*SfU*SmUfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOnRSOSSSOSSSSnSOSSnR
WV-44195	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmC*SfC*SfUn001RmUfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOnRSOSSnROSSSSnSOSSnR
WV-	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*Sf	CCCAGCAGCUUCAGUC	nRSSSSOSSSSnRSOnRSO

44196	AfGn001RfU*SfCfC*SfC*SfUn001RfUfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCUUUCUUIUCGAU	SSnROSSSSnSOSSnR
WV-44197	mCn001RmC*SmC*SfA*SfG*SfCfA*SfG*SfC*SfU*SfUn001RfC*SfAfG*SfU*SfCfC*SfC*SfUn001RfUfU*SfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSSSnRSOSSOSSnROSSSSnSOSSnR
WV-44228	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfCfCn001RfUfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSnRSSSOnROnRSSSSnSSSSnR
WV-44229	mCn001RmC*SmC*SfA*SfG*SfC*SfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfCfCn001RfUfUn001RfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSSSSSSnRSSnRSSOnROnRSSSSnSSSSnR
WV-44220	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfAn001RfG*SfU*SfC*SfC*RfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSnRSSSRSSSSSSSnSSSSnR
WV-44221	mCn001RmC*SmC*SfA*SfG*SfC*RfA*SfG*SfC*SfU*SfUn001RfC*SfA*SfGn001RfU*SfC*SfC*SfC*SfU*SfU*SfU*SfC*SfU*Sb001A*SIn001SmU*SfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU	nRSSSSRSSSSnRSSnRSSSSSSSSSnSSSSnR
WV-44478	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb001A*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTAIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44476	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*SfU*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44479	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44477	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*SfU*SCsm15*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCUCIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44480	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*SCsm15*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTCIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44481	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR

WV-44483	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-44486	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnROSnROSSSnROOSSSnSOSSnR
WV-44488	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROSnROSSSnROOSSSnSOSSnR
WV-44489	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROSSSnROOSSSnSOSSnR
WV-44490	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROSSOnROOSSSnSOSSnR
WV-44491	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmCfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSOnROOSSSnSOSSnR
WV-44492	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmUfUn001RmCfA*SfGn001RfUmCfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROSnROOSOnROOSSSnSOSSnR
WV-44493	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmUfUn001RmCfAfGn001RfUmCfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROOnROOSOnROOSSSnSOSSnR
WV-44494	mCn001RmC*SmC*SfA*SfG*SmCmAmGfCmUfUn001RmCfAmGn001RfUmCfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOOOOnROOnROOSOnROOSSSnSOSSnR
WV-44495	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44496	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SmUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44497	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCmAfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROOnROSSSnRSOSSSnSOSSnR

WV-44498	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44499	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RmUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44500	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SmCfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOSnRSOSSSnSOSSnR
WV-44501	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmCfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSOnRSOSSSnSOSSnR
WV-44502	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SmUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-44503	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-44505	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUfU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44506	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfC*SfC*SfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnRSOnRSSSSSOSSSSnSOSSnR
WV-44507	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmC*SfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnRSOnROOSSSOSSSSnSOSSnR
WV-44508	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmCfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnRSOnROOOSSOSSSSnSOSSnR
WV-44509	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RfC*SfAfGn001RfU*SmCmCfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnRSOnRSOOSSOSSSSnSOSSnR
WV-44510	mCn001RmC*SmC*SfA*SfG*SmCfA*SfG*SmCmUfUn001RmCfAfGn001RmUmCfC*SfC*SmUmUfU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOOnROOnROOSSOOSSSSnSOSSnR

WV-44511	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmU*SmUn001RfC*SfAmGn001RmUfC*SfC*SmCmUmUfU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnRSOnROSSOOOSSSSnSOSSnR
WV-44512	mCn001RmC*SmC*SfA*SfG*SmCmAmGfC*SfU*SfUn001RfC*SfAfGn001RfUmCmCfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOOSSnRSOnROOOSSOSSSSnSOSSnR
WV-44513	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfU*SfCmCmCmUmUfU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSSnRSOnRSOOOOOSSSSnSOSSnR
WV-44514	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSSOSSSnSOSSnR
WV-44515	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46416	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmU*SmUn001RmCmA*SmGn001RmUmCmC*SmC*SmU*SmUmUmC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOSnROSnROOSSSOOSSSnSOSSnR
WV-46417	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnRSOSSSnSOSSnR
WV-46418	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-46419	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RfUmC*SmCfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOSnRSOSSSnSOSSnR
WV-46420	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SmCfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOSnRSOSSSnSOSSnR
WV-46421	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSnROOSSSnSOSSnR
WV-46422	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SmCmCfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOOnRSOSSSnSOSSnR

WV-46423	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SmCmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOOnROOSSSnSOSSnR
WV-46424	mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOOnROOSSSnSOSSnR
WV-46425	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SmCmU*SmUn001RmCfA*SfGn001RmUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSOOnROOSSSnSOSSnR
WV-46426	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSOnROOSSSnSOSSnR
WV-46427	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSOOnROOSSSnSOSSnR
WV-46428	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RmUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSOnROOSSSnSOSSnR
WV-46429	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RmCfA*SfGn001RfUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSOnROOSSSnSOSSnR
WV-46430	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmUfUn001RmCfA*SfGn001RfUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROSnROSOOnROOSSSnSOSSnR
WV-46431	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RmUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSOOnROOSSSnSOSSnR
WV-46432	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RmCfA*SfGn001RmUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSOnROOSSSnSOSSnR
WV-46433	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmUfUn001RmCfA*SfGn001RmUmC*SfC*SmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROSnROSSOnROOSSSnSOSSnR
WV-46434	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUmUn001RmCfA*SfGn001RmUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSOOnROOSSSnSOSSnR

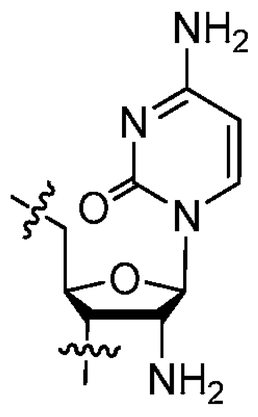
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WV-46436	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SmCmUmUn001RmCfA*SfGn001RmUmC*SmCmCmUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSOOnROSnROSOOnROOSSSnSOSSnR
WV-46437	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RTeo	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46438	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46439	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SGeo*SAeon001RTeo	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAT	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
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WV-46443	mCn001RmC*SmC*SfA*SfG*Sm5CeomA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
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WV-46446	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001Rm5CeofA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR

WV-46447	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUm5Ceo*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46448	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*STeomUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUTUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46449	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUTCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
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WV-46464	mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SrUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOSSOSnROSnROSSSSOOSSSnSOSSnR
WV-46465	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SUsm15fC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR

WV-46466	mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SrUfC*SmG*SmAn001RmU	CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU	nRSSSSOOSSOnROSnROSSSnROOSSSnSOSSnR
WV-48444	mG*mAfAfGfCfUfGfCfUfGmG*mG	GAAGCUGCUGGG	XOOOOOOOOOX
WV-48445	mG*mAmAmGmCmUmGmCmUmGmG*mG	GAAGCUGCUGGG	XOOOOOOOOOX
WV-48446	mG*mArArGrCrUrGrCrUrGmG*mG	GAAGCUGCUGGG	XOOOOOOOOOX
WV-48447	mC*mUfGfAfAfGfCfUfGfCfUfGmG*mG	CUGAAGCUGCUGGG	XOOOOOOOOOOOX
WV-48448	mC*mUmGmAmAmGmCmUmGmCmUmGmG*mG	CUGAAGCUGCUGGG	XOOOOOOOOOOOX
WV-48449	mC*mUrGrArArGrCrUrGrCrUrGmG*mG	CUGAAGCUGCUGGG	XOOOOOOOOOOOX
WV-48450	mG*mAfCfUfGfAfAfGfCfUfGfCfUfGmG*mG	GACUGAAGCUGCUGGG	XOOOOOOOOOOOOOX
WV-48451	mG*mAmCmUmGmAmAmGmCmUmGmCmUmGmG*mG	GACUGAAGCUGCUGGG	XOOOOOOOOOOOOOX
WV-48452	mG*mArCrUrGrArArGrCrUrGrCrUrGmG*mG	GACUGAAGCUGCUGGG	XOOOOOOOOOOOOOX

Notes:

Description, Base Sequence and Stereochemistry/Linkage, due to their length, may be divided into multiple lines in Table 1 (e.g., Table 1A, Table 1B, Table 1C, etc.). Unless otherwise specified, all oligonucleotides in Table 1 are single-stranded. As appreciated by those skilled in the art, nucleoside units are unmodified and contain unmodified nucleobases and 2'-deoxy sugars unless otherwise indicated (e.g., with r, m, m5, eo, etc.); linkages, unless otherwise indicated, are natural phosphate linkages; and acidic/basic groups may independently exist in their salt forms. If a sugar is not specified, the sugar is a natural DNA sugar; and if an internucleotidic linkage is not specified, the internucleotidic linkage is a natural phosphate linkage. Moieties and modifications:

a: 2'-NH_2 (e.g., aC: );

m: 2'-OMe;

m5: methyl at 5-position of C (nucleobase is 5-methylcytosine);

m5lC: methyl at 5-position of C (nucleobase is 5-methylcytosine) and sugar is a LNA sugar;

l: LNA sugar;

I: nucleobase is hypoxanthine;

f: 2'-F;

r: 2'-OH;

eo: 2'-MOE (2'−$OCH_2CH_2OCH_3$);

m5Ceo: 5-methyl 2'-O-methoxyethyl C;

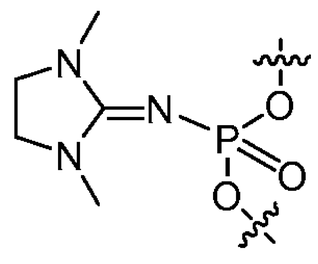
O, PO: phosphodiester (phosphate). It can a linkage or be an end group (or a component thereof), e.g., a linkage between a linker and an oligonucleotide chain, an internucleotidic linkage (a natural phosphate linkage), etc. Phosphodiesters are typically indicated with "O" in the Stereochemistry/Linkage column and are typically not marked in the Description column (if it is an end group, e.g., a 5'-end group, it is indicated in the Description and typically not in Stereochemistry/Linkage); if no linkage is indicated in the Description column, it is typically a phosphodiester unless otherwise indicated. Note that a phosphate linkage between a linker (e.g., L001) and an oligonucleotide chain may not be marked in the Description column, but may be indicated with "O" in the Stereochemistry/Linkage column;

*, PS: Phosphorothioate. It can be an end group (if it is an end group, e.g., a 5'-end group, it is indicated in the Description and typically not in Stereochemistry/Linkage), or a linkage, e.g., a linkage between linker (e.g., L001) and an oligonucleotide chain, an internucleotidic linkage (a phosphorothioate internucleotidic linkage), etc.;

R, *R*p: Phosphorothioate in the *R*p configuration. Note that * R in Description indicates a single phosphorothioate linkage in the *R*p configuration;

S, *S*p: Phosphorothioate in the *S*p configuration. Note that * S in Description indicates a single phosphorothioate linkage in the *S*p configuration;

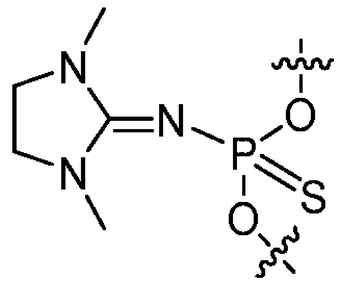
X: stereorandom phosphorothioate;

n001:  ;

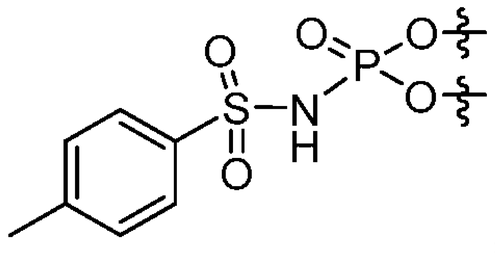
nX (when utilized or n001): stereorandom n001;

nR (when utilized or n001) or n001R: n001 in Rp configuration;

nS (when utilized or n001) or n001S: n001 in Sp configuration;

*n001:  ;

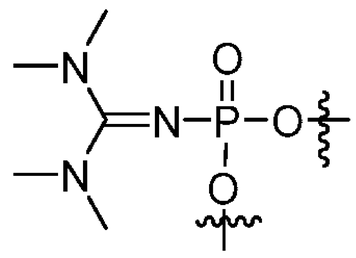
n*X: stereorandom *n001;

n002:  ;

nX (when utilized for n002): stereorandom n002;

nR (when utilized for n002) or n002R: n002 in Rp configuration;

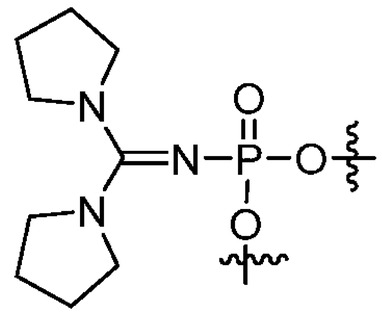
nS (when utilized for n002) or n002S: n002 in Sp configuration;

n003:  ;

nX (when utilized for n003): stereorandom n003;

nR (when utilized for n003) or n003R: n003 in Rp configuration;

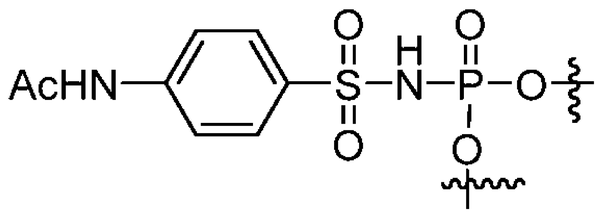
nS (when utilized for n003) or n003S: n003 in Sp configuration;

n004:  ;

nX (when utilized for n004): stereorandom n004;

nR (when utilized for n004) or n004R: n004 in Rp configuration;

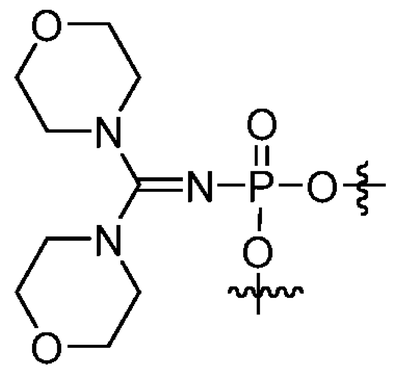
nS (when utilized for n004) or n004S: n004 in Sp configuration;

n006:  ;

nX (when utilized for n006): stereorandom n006;

nR (when utilized for n006) or n006R: n006 in Rp configuration;

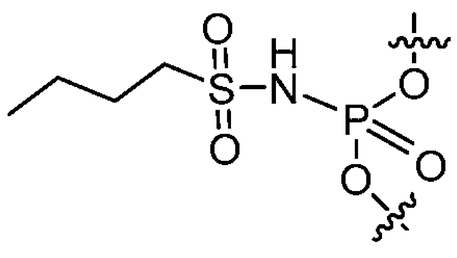
nS (when utilized for n006) or n006S: n006 in Sp configuration;

n008:  ;

nX (when utilized for n008): stereorandom n008;

nR (when utilized for n008) or n008R: n008 in Rp configuration;

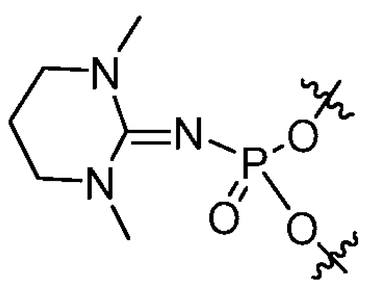
nS (when utilized for n008) or n008S: n008 in Sp configuration;

n020:  ;

nX (when utilized for n020): stereorandom n020;

nR (when utilized for n020) or n020R: n020 in Rp configuration;

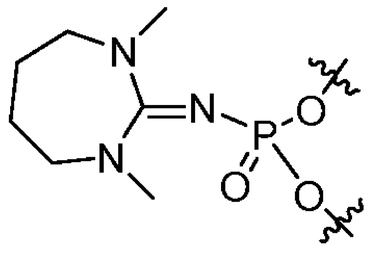
nS (when utilized for n020) or n020S: n020 in Sp configuration;

n025:  ;

nX (when utilized or n025): stereorandom n025;

nR (when utilized or n025) or n025R: n025 in Rp configuration;

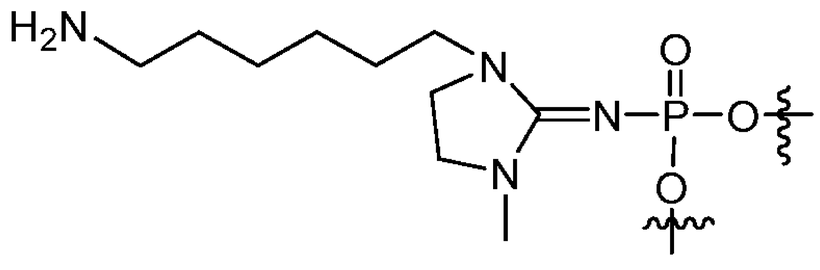
nS (when utilized or n025) or n025S: n025 in Sp configuration;

n026  ;

nX (when utilized or n026): stereorandom n026;

nR (when utilized or n026) or n026R: n026 in Rp configuration;

nS (when utilized or n026) or n026S: n026 in Sp configuration;

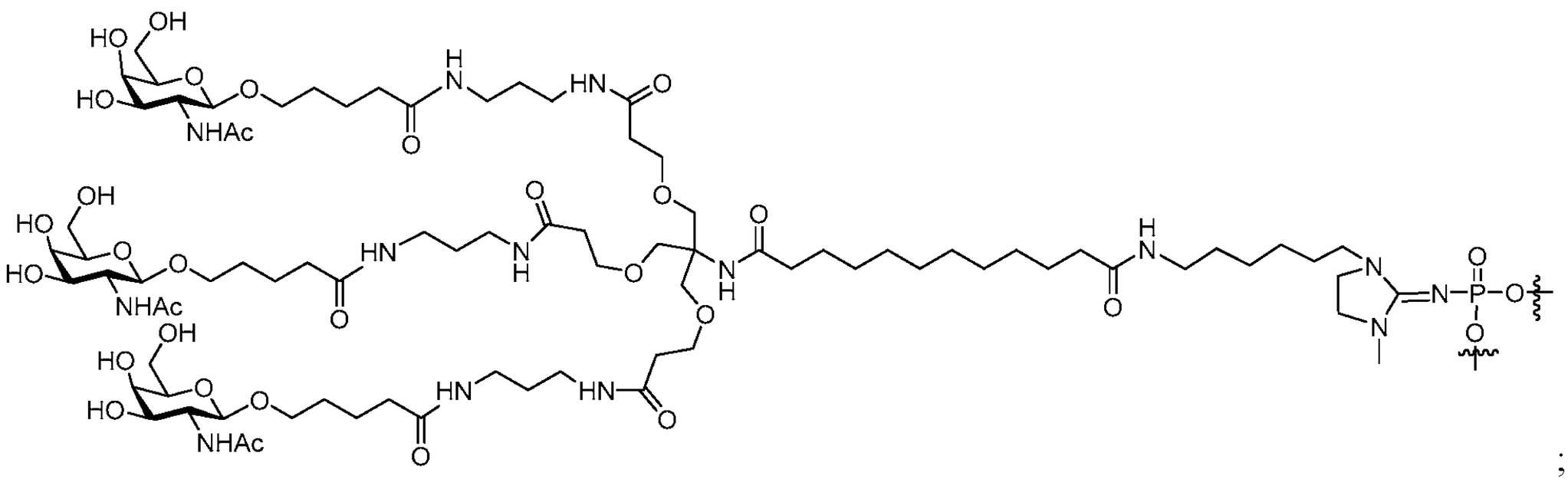
n051:  ;

nX (when utilized for n051): stereorandom n051;

nR (when utilized for n051) or n051R: n051 in Rp configuration;

nS (when utilized for n051) or n051S: n051 in Sp configuration;

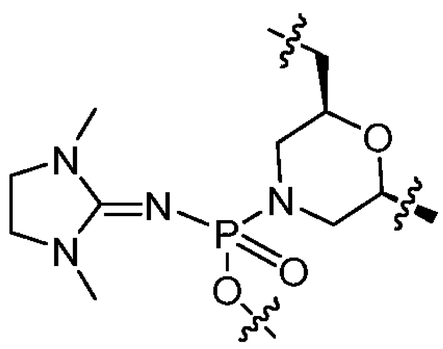
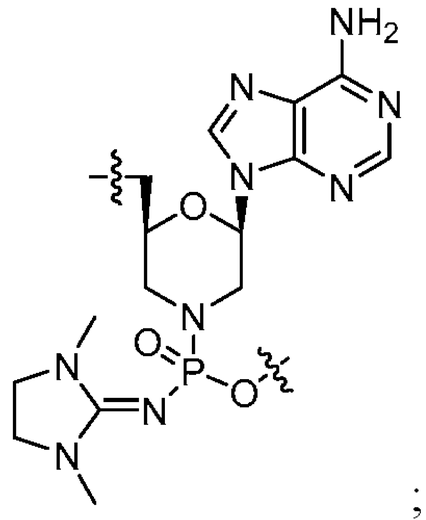
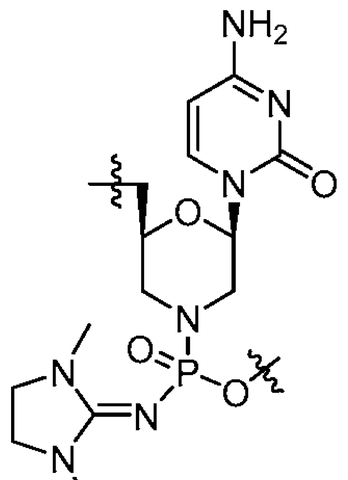
n057:

 ;

nX (when utilized for n057): stereorandom n057;

nR (when utilized for n057) or n057R: n057 in Rp configuration;

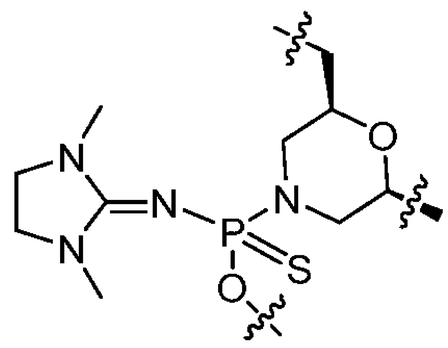
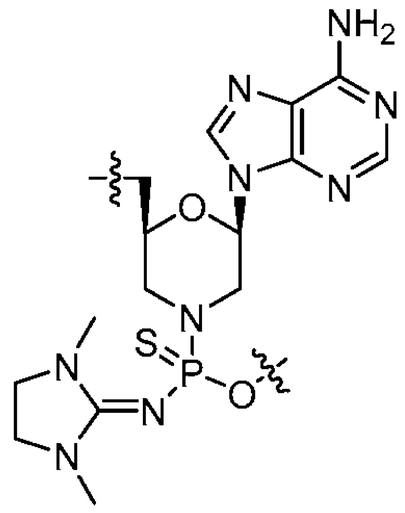
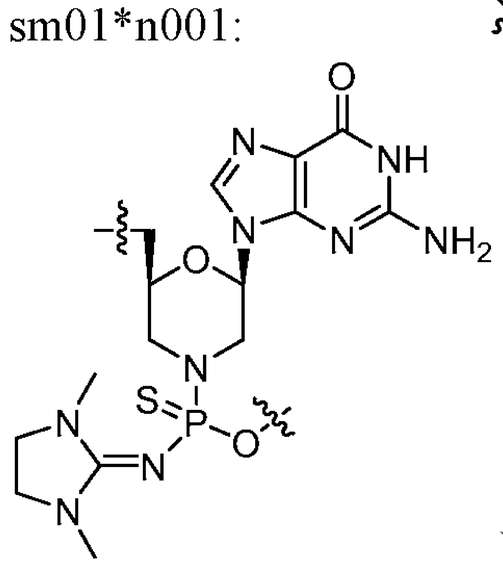
nS (when utilized for n057) or n057S: n057 in Sp configuration;

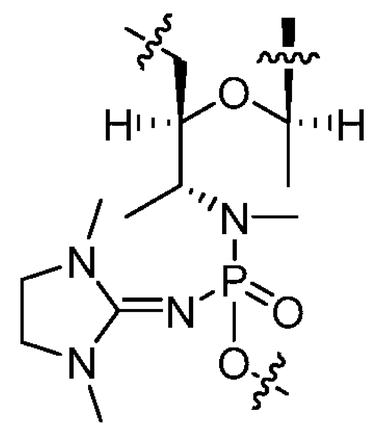
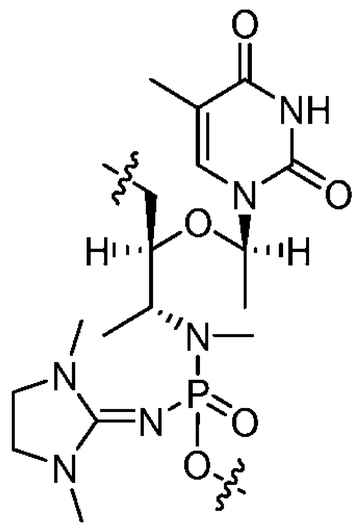
sm01n001:  ; (e.g., Asm01n001:  ; Gsm01n001: 

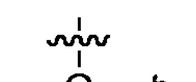
\ ; Tsm01n001: 

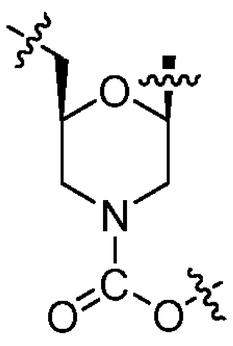
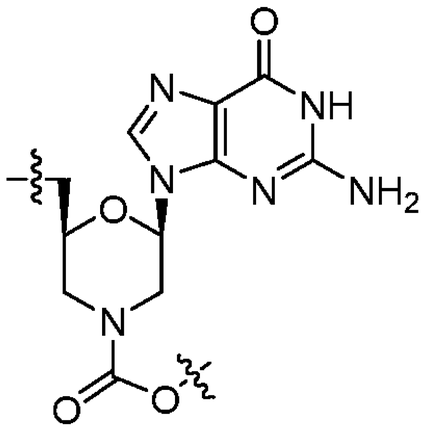
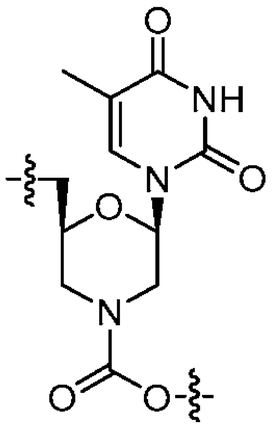
\ ; Csm01n001: 

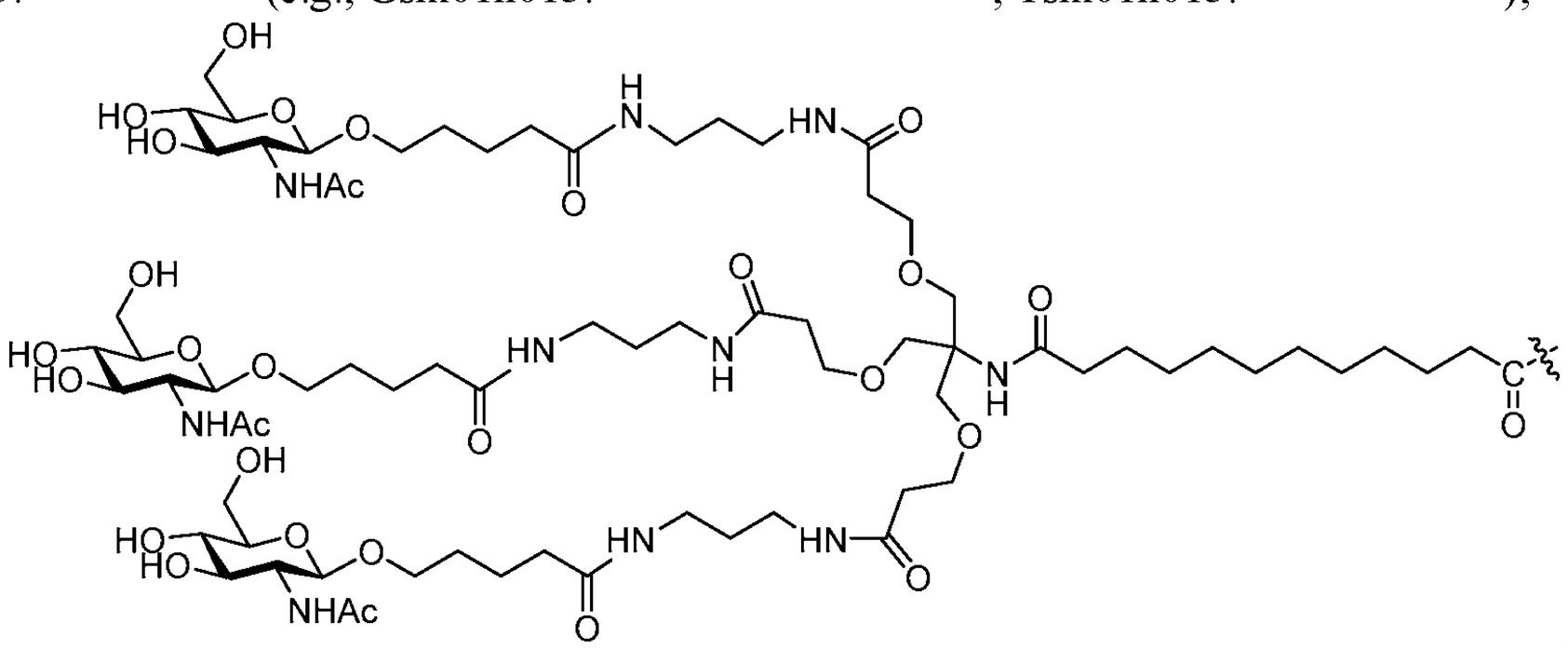
\ );

sm01*n001:  (e.g., Asm01*n001:  ; Gsm01*n001: );

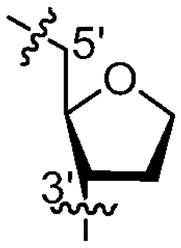
sm18n001:  (e.g., Tsm18n001: );

n013: n013:  , wherein −C(O)− is bonded to nitrogen; as utilized in the Table, n013 may be indicated as O in Stereochemistry/ Linkage;

sm01n013:  (e.g., Gsm01n013:  ; Tsm01n013: );

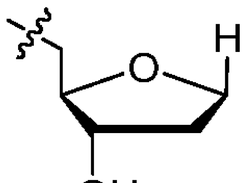
Mod001:  ;

L001: −NH−$(CH_2)_6$− linker (C6 linker, C6 amine linker or C6 amino linker), connected to Mod (e.g., Mod001) through −NH−, and, in the case of, for example, WV-27457, the 5'-end of the oligonucleotide chain through a phosphate linkage (O or PO). For example, in WV-27457, L001 is connected to Mod001 through –NH− (forming an amide group –C(O)−NH−), and is connected to the oligonucleotide chain through a phosphate linkage (O);

L010: 

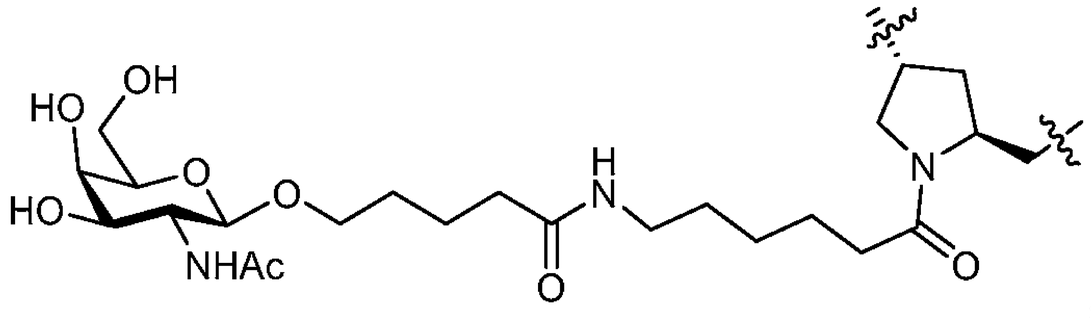
. In some embodiments, when L010 is present in the middle of an oligonucleotide, it is bonded to internucleotidic linkages as other sugars (e.g., DNA sugars), e.g., its 5'-carbon is connected to another unit (e.g., 3' of a sugar) and its 3'-carbon is connected to another unit (e.g., a 5'-carbon of a carbon) independently, e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

L012:−$CH_2CH_2OCH_2CH_2OCH_2CH_2$−. When L012 is present in the middle of an oligonucleotide, each of its two ends is independently bonded to an internucleotidic linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

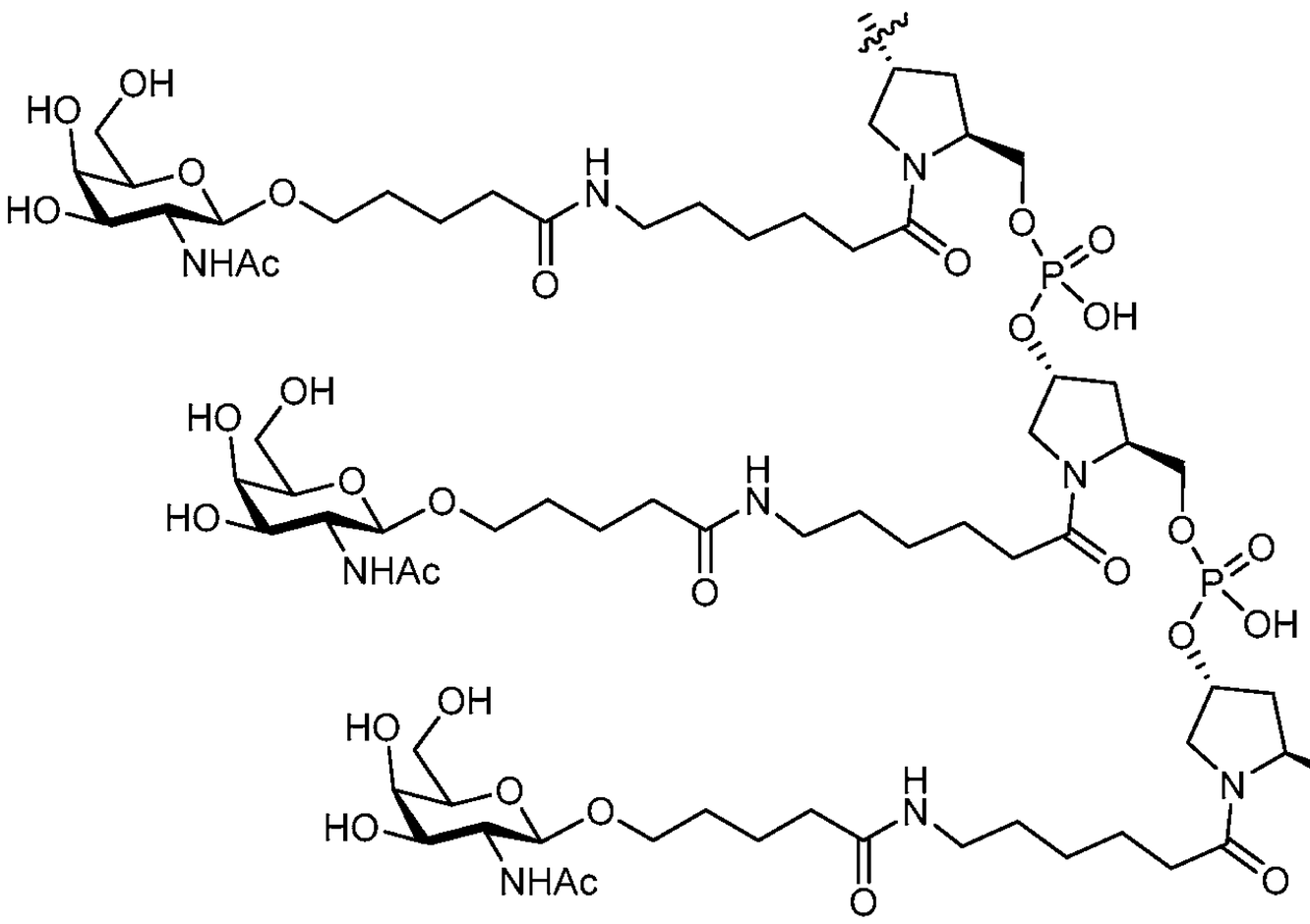
L022: 

, wherein L022 is connected to the rest of a molecule through a phosphate unless indicated otherwise, for example, in WV-42488 through a *R*p phosphorothioate;

L023: HO−$(CH_2)_6$−, wherein CH_2 is connected to the rest of a molecule through a phosphate unless indicated otherwise. For example, in WV-39202 (wherein the **O** in OnRnRnRnRSSSSSSSSSSSSSSSSSSSnRSSSSSnRSSnR indicates a phosphate linkage connecting L023 to the rest of the molecule);

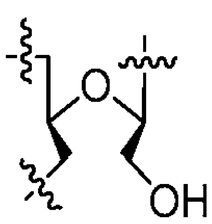
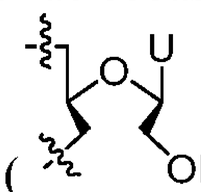
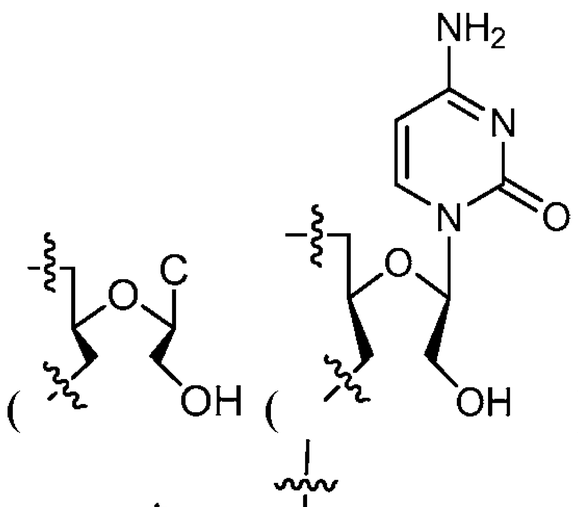
L025: 

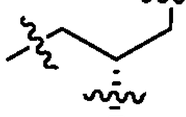
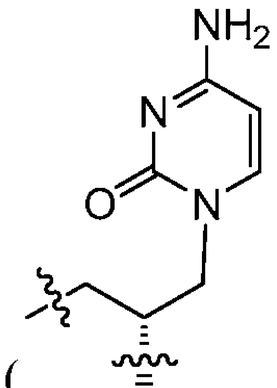
, wherein the −CH_2− connection site is utilized as a C5 connection site of a sugar (e.g., a DNA sugar) and is connected to another unit (e.g., 3' of a sugar), and the connection site on the ring is utilized as a C3 connection site and is connected to another unit (e.g., a 5'-carbon of a carbon), each of which is independently, e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p))). When L025 is at a5'-end without any modifications, its −CH_2− connection site is bonded to −OH. For example, L025L025L025− in various oligonucleotides has the structure of

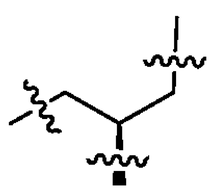


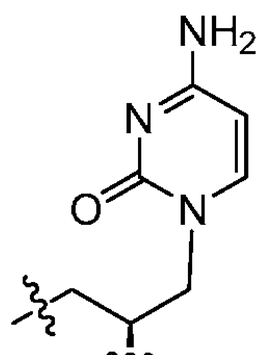
(may exist as various salt forms) and is connected to 5'-carbon of an oligonucleotide chain via a linkage as indicated (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

L028:$-CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2-$. When L028 is present in the middle of an oligonucleotide, each of its two ends is independently bonded to an internucleotidic linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

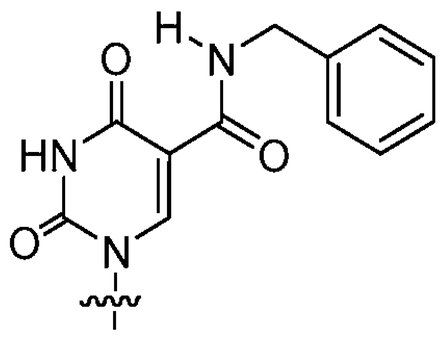
sm04:  . sm04 follows a nucleobase to which it is bonded; for example, in WV-28787, "Usm04" indicates that U is bonded to sm04 (); in WV-44238, "Csm04" indicates that C is bonded to sm04 ());

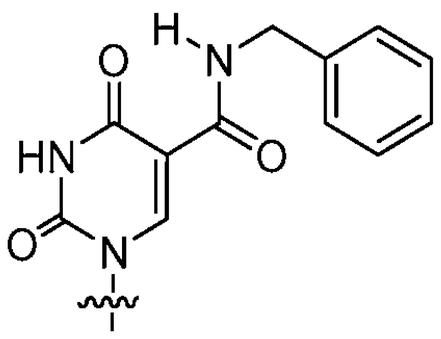
sm11:  . sm11 follows a nucleobase to which it is bonded; for example, in WV-47403, "Csm11" indicates that C is bonded to sm11 ();

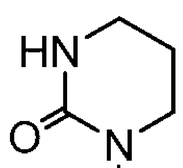
sm12:  . sm12 follows a nucleobase to which it is bonded; for example, in WV-47402, "Csm12"



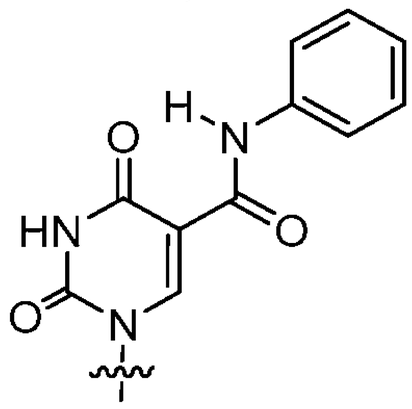
indicates that C is bonded to sm12 ();
a: 2'-NH_2;

b001U: a nucleoside whose base is  ;

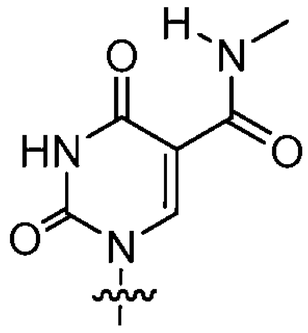
b001rU: a nucleoside whose base is  , and whose sugar is a natural RNA sugar (r);



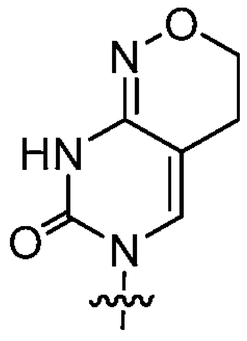
b002U: a nucleoside whose base is  ;



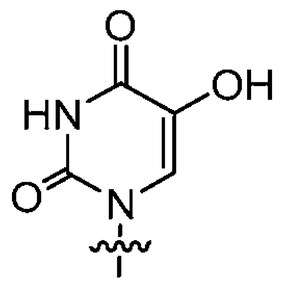
b003U: a nucleoside whose base is ;

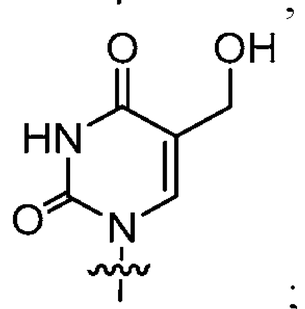


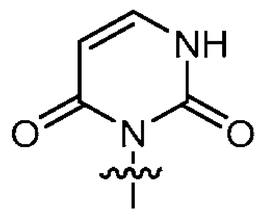
b004U: a nucleoside whose base is ;

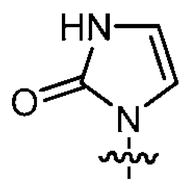


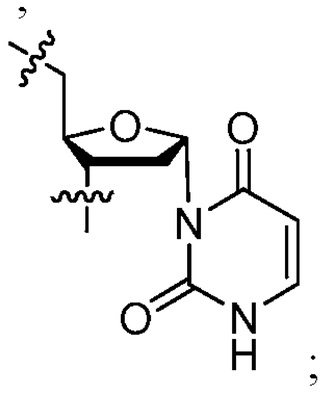
b005U: a nucleoside whose base is ;

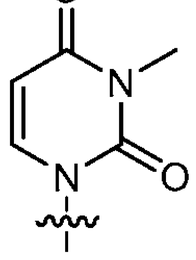
b006U: a nucleoside whose base is  ;

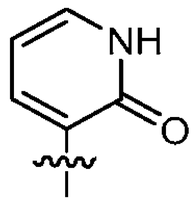
b007U: a nucleoside whose base is  ;

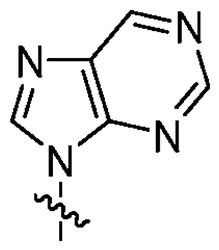
b008U: a nucleoside whose base is  ;

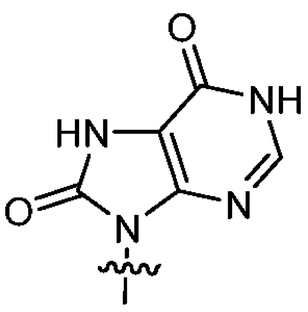
b009U: a nucleoside whose base is  ;

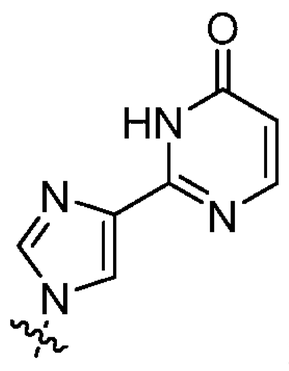
b010U: a nucleoside having the structure of  ;

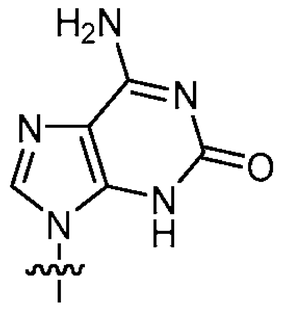
b011U: a nucleoside whose base is  ;

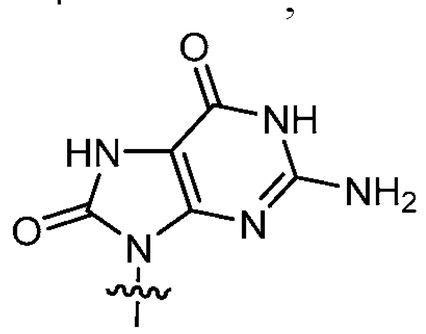
b012U: a nucleoside whose base is  ;

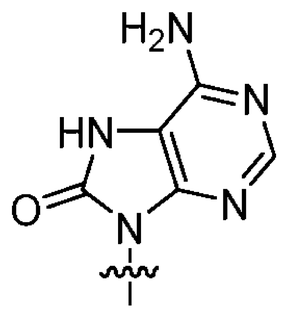
b003I: a nucleoside whose base is  ;

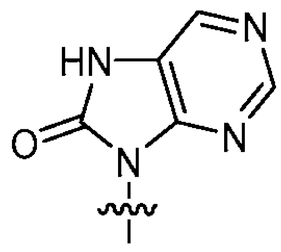
b004I: a nucleoside whose base is  ;

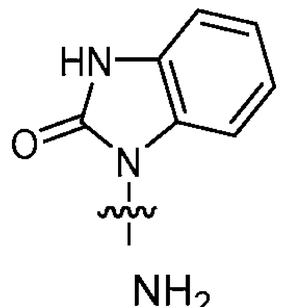
b014I: a nucleoside whose base is  ;

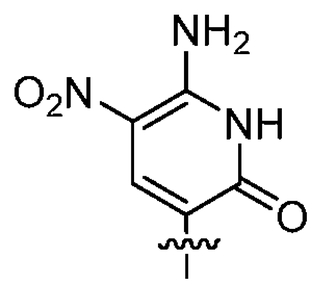
b001G: a nucleoside whose base is  ;

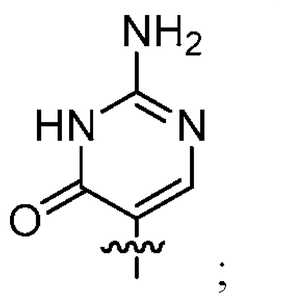
b002G: a nucleoside whose base is  ;

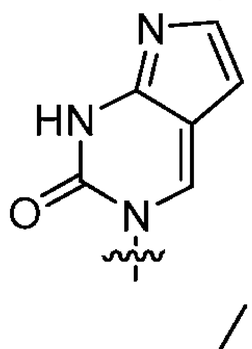
b001A: a nucleoside whose base is  ;

b002A: a nucleoside whose base is  ;

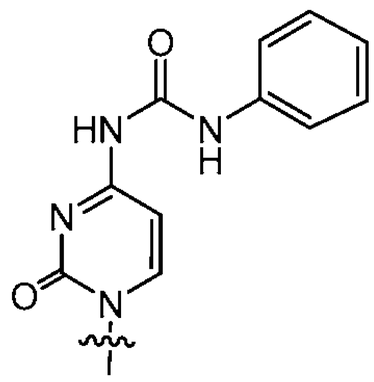
b003A: a nucleoside whose base is  ;

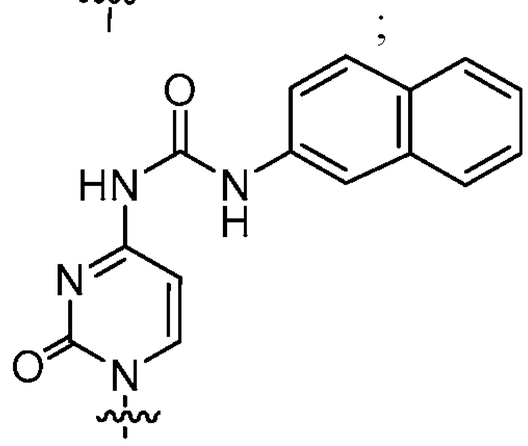
zdnp: a nucleoside whose base is  ;

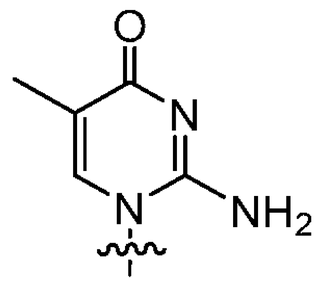
b001C: a nucleoside whose base is  ;

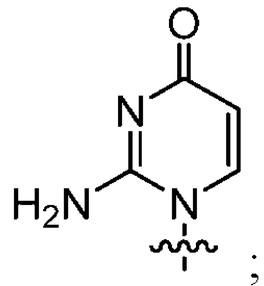
b002C: a nucleoside whose base is  ;

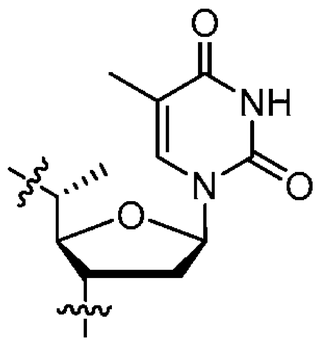
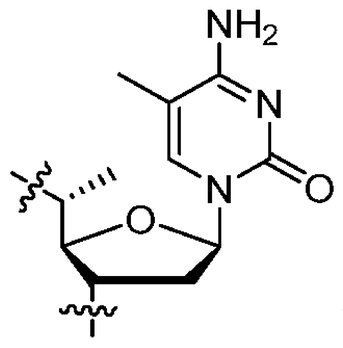
b003C: a nucleoside whose base is  ;

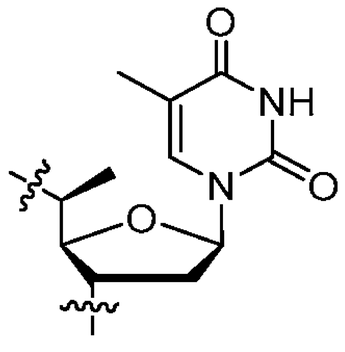
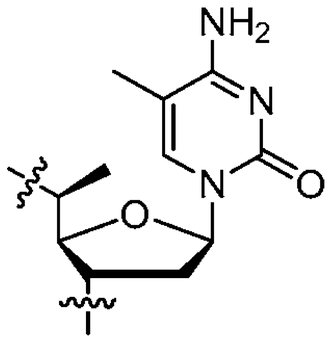
b004C: a nucleoside whose base is  ;

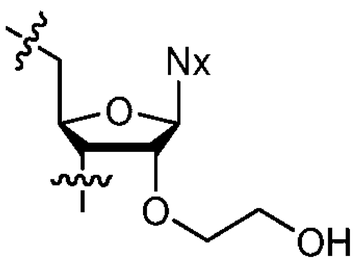
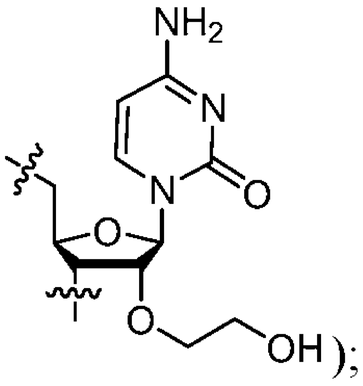
b007C: a nucleoside whose base is  ;

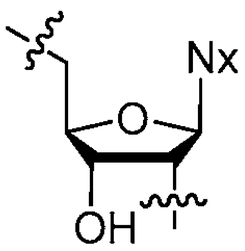
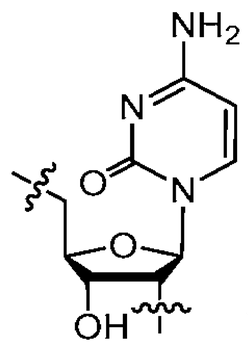
b008C: a nucleoside whose base is  ;

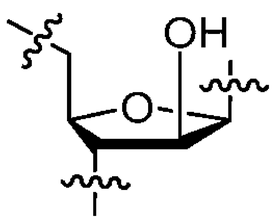
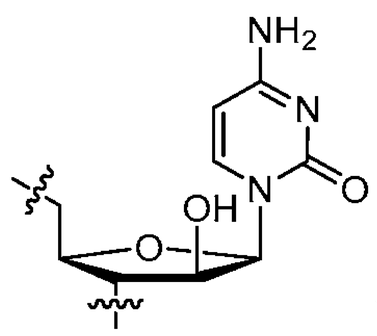
b009C: a nucleoside whose base is  ;

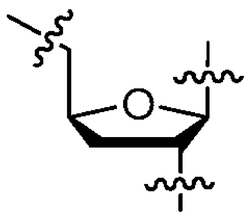
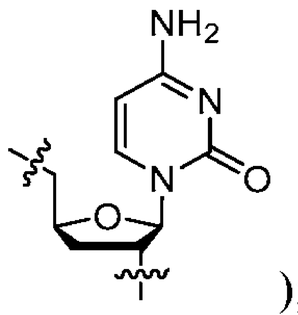
5MR: 5’-Me modification to a sugar, and configuration of the 5’-carbon the sugar is *R* (e.g., 5MRdT  ; 5MRm5dC: );

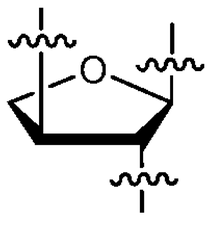
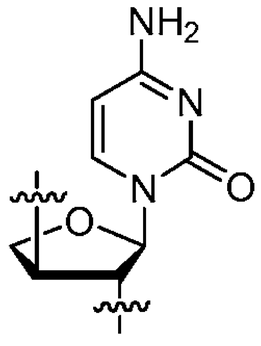
5MS: 5’-Me modification to a sugar, and configuration of the 5’-carbon the sugar is *S* (e.g., 5MSdT:  ; 5MSm5dC: );

rNxsm13:  , wherein Nx is a nucleobase (e.g., rCsm13: );

rNxsm14:  , wherein Nx is a nucleobase (e.g., rCsm14: );

sm15:  . sm15 follows a nucleobase to which it is bonded (e.g., Csm15: );

sm16:  . sm16 follows a nucleobase to which it is bonded (e.g., Csm16: ); and

sm17:  . sm17 follows a nucleobase to which it is bonded (e.g., Csm17: ).

In some embodiments, a sugar is bonded to an internucleotidic linkage through an oxygen atom, e.g., an oxygen atom in a natural phosphate linkage such as in typical natural DNA molecules. In some embodiments, a sugar is boned to an internucleotidic linkage through an atom that is not oxygen. In some embodiments, a sugar is boned to an internucleotidic linkage through a nitrogen atom of a sugar. In some embodiments, a sugar is boned to an internucleotidic linkage through a ring nitrogen atom of a sugar (e.g., in sm01); in such cases, a ring nitrogen atom of a sugar may directly form a bond with a linkage phosphorus atom (e.g., see sm01n001), and those skilled in the art will appreciate an oxygen atom may be removed from a linkage (e.g., see sm01n001). For examples, see also sm18, which as shown in oligonucleotides in the Tables, can directly bond to linkage phosphorus through a nitrogen atom (e.g., sm18n001). Certain reagents (e.g., phosphoramidites, nucleosides, etc.) and methods for utilizing various modifications, e.g., those exemplified in the Tables herein, such as modified sugars, modified nucleobases, etc., are described in the Examples or WO 2021/071858 which is incorporated herein by reference.

Oligonucleotide Compositions

[00635] Among other things, the present disclosure provides various oligonucleotide compositions. In some embodiments, the present disclosure provides oligonucleotide compositions of oligonucleotides described herein. In some embodiments, an oligonucleotide composition comprises a plurality of oligonucleotides described in the present disclosure. In some embodiments, an oligonucleotide composition is chirally controlled. In some embodiments, an oligonucleotide composition is not chirally controlled

(stereorandom).

[00636] Linkage phosphorus of natural phosphate linkages is achiral. Linkage phosphorus of many modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are chiral. In some embodiments, during preparation of oligonucleotide compositions (e.g., in traditional phosphoramidite oligonucleotide synthesis), configurations of chiral linkage phosphorus are not purposefully designed or controlled, creating non-chirally controlled (stereorandom) oligonucleotide compositions (substantially racemic preparations) which are complex, random mixtures of various stereoisomers (diastereoisomers) - for oligonucleotides with n chiral internucleotidic linkages (linkage phosphorus being chiral), typically 2n stereoisomers (e.g., when n is 10, 210 =1,032; when n is 20, 220 = 1,048,576). These stereoisomers have the same constitution, but differ with respect to the pattern of stereochemistry of their linkage phosphorus.

[00637] In some embodiments, stereorandom oligonucleotide compositions have sufficient properties and/or activities for certain purposes and/or applications. In some embodiments, stereorandom oligonucleotide compositions can be cheaper, easier and/or simpler to produce than chirally controlled oligonucleotide compositions. However, stereoisomers within stereorandom compositions may have different properties, activities, and/or toxicities, resulting in inconsistent therapeutic effects and/or unintended side effects by stereorandom compositions, particularly compared to certain chirally controlled oligonucleotide compositions of oligonucleotides of the same constitution.

[00638] In some embodiments, the present disclosure encompasses technologies for designing and preparing chirally controlled oligonucleotide compositions. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions, e.g., of many oligonucleotides in Table 1 which contain S and/or R in their stereochemistry/linkage. In some embodiments, a chirally controlled oligonucleotide composition comprises a controlled/pre-determined (not random as in stereorandom compositions) level of a plurality of oligonucleotides, wherein the oligonucleotides share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages). In some embodiments, the oligonucleotides share the same pattern of backbone chiral centers (stereochemistry of linkage phosphorus). In some embodiments, a pattern of backbone chiral centers is as described in the present disclosure. In some embodiments, oligonucleotides of a plurality are structural identical.

[00639] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages").

[00640] In some embodiments, the present disclosure provides an oligonucleotide composition comprising

a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence, for oligonucleotides of the plurality.

[00641] In some embodiments, an oligonucleotide composition is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common pattern of backbone linkages, and

the same linkage phosphorus stereochemistry at one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality.

[00642] In some embodiments, an oligonucleotide composition is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common patter of backbone linkages, and

a common pattern of backbone chiral centers, which pattern comprises at least one Sp,

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality.

[00643] In some embodiments, an oligonucleotide composition is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common patter of backbone linkages, and

a common pattern of backbone chiral centers, which pattern comprises at least one Rp,

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality.

[00644] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

1) a common constitution, and

2) share the same linkage phosphorus stereochemistry at one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more) chiral

internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides of the common constitution, for oligonucleotides of the plurality.

[00645] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein stereochemical purity of the linkage phosphorus of each chirally controlled internucleotidic linkage is independently 80%-100% (e.g., 85-100%, 90-100%, about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%).

[00646] In some embodiments, an oligonucleotide composition is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common pattern of backbone linkages, and

the same linkage phosphorus stereochemistry at one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein stereochemical purity of the linkage phosphorus of each chirally controlled internucleotidic linkage is independently 80%-100% (e.g., 85-100%, 90-100%, about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%).

[00647] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

1) a common constitution, and

2) share the same linkage phosphorus stereochemistry at one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more) chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein stereochemical purity of the linkage phosphorus of each chirally controlled internucleotidic linkage is independently 80%-100% (e.g., 85-100%, 90-100%, about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%).

[00648] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-

40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

[00649] In some embodiments, the present disclosure provides an oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence of each plurality is independently complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

[00650] In some embodiments, the present disclosure provides an composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality; and

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

[00651] In some embodiments, as described herein a portion can be about or at least about 10-40, 15-40, 20-40, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, nucleobases long. In some embodiments, a portion is about or at least about or no more than about 1%-50% of a nucleic acid. In some embodiments, a portion is the whole length of a nucleic acid. In some embodiments, a common base sequence is complementary to a base sequence of a portion of a nucleic acid as described herein. In some embodiments, it is fully complementary across its length except at a nucleobase opposite to a target adenosine. In some embodiments, it is fully complementary across its length. In some embodiments, a target adenosine is associated with a condition, disorder or disease. In some embodiments, a target adenosine is a G to A mutation associated with a condition, disorder or disease. In some embodiments, a target adenosine is edited

to I by a provided oligonucleotide or composition. In some embodiments, as described herein editing increases expression, level and/or activity of a transcript or a product thereof (e.g., a mRNA, a protein, etc.). In some embodiments, as described herein editing reduces expression, level and/or activity of a transcript or a product thereof (e.g., a mRNA, a protein, etc.).

[00652] In some embodiments, oligonucleotide of a plurality share the same nucleobase modifications and/or sugar modifications. In some embodiments, oligonucleotide of a plurality share the same internucleotidic linkage modifications (wherein the internucleotidic linkages may be in various acid, base, and/or salt forms). In some embodiments, oligonucleotides of a plurality share the same nucleobase modifications, sugar modifications, and internucleotidic linkage modifications, if any. In some embodiments, oligonucleotides of a plurality are of the same form, e.g., an acid form, a base form, or a particularly salt form (e.g., a pharmaceutically acceptable salt form, e.g., salt form). In some embodiments, oligonucleotides in a composition may exist as one or more forms, e.g., acid forms, base forms, and/or one or more salt forms. In some embodiments, in an aqueous solution (e.g., when dissolved in a buffer like PBS), anions and cations may dissociate. In some embodiments, oligonucleotides of a plurality are of the same constitution. In some embodiments, oligonucleotides of a plurality are structurally identical. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides are of a common constitution, and share the same linkage phosphorus stereochemistry at one or more (e.g., 1-60, 1-50, 1-40, 1-30, 1-25, 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 or more) chiral internucleotidic linkages (chirally controlled internucleotidic linkages), wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides of the common constitution, for oligonucleotides of the plurality.

[00653] In some embodiments, at least one chiral internucleotidic linkage is chirally controlled. In some embodiments, at least 2 internucleotidic linkages are independently chirally controlled. In some embodiments, the number of chirally controlled internucleotidic linkages is at least 3. In some embodiments, it is at least 4. In some embodiments, it is at least 5. In some embodiments, it is at least 6. In some embodiments, it is at least 7. In some embodiments, it is at least 8. In some embodiments, it is at least 9. In some embodiments, it is at least 10. In some embodiments, it is at least 11. In some embodiments, it is at least 12. In some embodiments, it is at least 13. In some embodiments, it is at least 14. In some embodiments, it is at least 15. In some embodiments, it is at least 20. In some embodiments, it is at least 25. In some embodiments, it is at least 30.

[00654] In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%,

85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all internucleotidic linkages are chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all chiral internucleotidic linkages are chirally controlled. In some embodiments, at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all phosphorothioate internucleotidic linkages are chirally controlled. In some embodiments, a percentage is at least 50%. In some embodiments, a percentage is at least 60%. In some embodiments, a percentage is at least 70%. In some embodiments, a percentage is at least 80%. In some embodiments, a percentage is at least 90%. In some embodiments, a percentage is at least 90%. In some embodiments, each chiral internucleotidic linkage is chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage is chirally controlled.

[00655] In some embodiments, no more than 1-10, e.g., no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, chiral internucleotidic linkages are not chirally controlled. In some embodiments, no more than 1 chiral internucleotidic linkages is not chirally controlled. In some embodiments, no more than 2 chiral internucleotidic linkages are not chirally controlled. In some embodiments, no more than 3 chiral internucleotidic linkages are not chirally controlled. In some embodiments, no more than 4 chiral internucleotidic linkages are not chirally controlled. In some embodiments, no more than 5 chiral internucleotidic linkages are not chirally controlled. In some embodiments, the number of non-chirally controlled internucleotidic linkages is 1. In some embodiments, it is 2. In some embodiments, it is 3. In some embodiments, it is 4. In some embodiments, it is 5.

[00656] In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides, wherein each oligonucleotide of the plurality is independently a particular oligonucleotide or a salt thereof. In some embodiments, the present disclosure provides a composition comprising a plurality of oligonucleotides, wherein each oligonucleotide of the plurality is independently a particular oligonucleotide or a pharmaceutically acceptable salt thereof. In some embodiments, such a composition is enriched relative to a substantially racemic preparation of a particular oligonucleotide. As appreciated by those skilled in the art, oligonucleotides of the plurality share a common sequence which is the base sequence of the particular oligonucleotide. In some embodiments, at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-

100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition that share the base sequence of a the particular oligonucleotide are oligonucleotide of the plurality. In some embodiments, at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition that share the constitution of the particular oligonucleotide or a salt thereof are oligonucleotide of the plurality. In some embodiments, a percentage is at least 10%. In some embodiments, a percentage is at least 20%. In some embodiments, a percentage is at least 30%. In some embodiments, a percentage is at least 40%. In some embodiments, a percentage is at least 50%. In some embodiments, it is at least 60%. In some embodiments, it is at least 70%. In some embodiments, it is at least 80%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%. In some embodiments, it is about 5-100%. In some embodiments, it is about 10-100%. In some embodiments, it is about 20-100%. In some embodiments, it is about 30-90%. In some embodiments, it is about 30-80%. In some embodiments, it is about 30-70%. In some embodiments, it is about 40-90%. In some embodiments, it is about 40-80%. In some embodiments, it is about 40-70%. In some embodiments, a particular oligonucleotide is an oligonucleotide exemplified herein, e.g., an oligonucleotide of Table 1 or another table.

[00657] In some embodiments, an enrichment relative to a substantially racemic preparation is that at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition, or all oligonucleotides in the composition that share the common base sequence of a plurality, or all oligonucleotides in the composition that share the common constitution of a plurality, are oligonucleotide of the plurality. In some embodiments, a percentage is at least 10%. In some embodiments, a percentage is at least 20%. In some embodiments, a percentage is at least 30%. In some embodiments, a percentage is at least 40%. In some embodiments, a percentage is at least 50%. In some

embodiments, it is at least 60%. In some embodiments, it is at least 70%. In some embodiments, it is at least 80%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%. In some embodiments, it is about 5-100%. In some embodiments, it is about 10-100%. In some embodiments, it is about 20-100%. In some embodiments, it is about 30-90%. In some embodiments, it is about 30-80%. In some embodiments, it is about 30-70%. In some embodiments, it is about 40-90%. In some embodiments, it is about 40-80%. In some embodiments, it is about 40-70%.

[00658] In some embodiments, at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition that share the common base sequence of a plurality are oligonucleotide of the plurality. In some embodiments, a percentage is at least 10%. In some embodiments, a percentage is at least 20%. In some embodiments, a percentage is at least 30%. In some embodiments, a percentage is at least 40%. In some embodiments, a percentage is at least 50%. In some embodiments, it is at least 60%. In some embodiments, it is at least 70%. In some embodiments, it is at least 80%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%. In some embodiments, it is about 5-100%. In some embodiments, it is about 10-100%. In some embodiments, it is about 20-100%. In some embodiments, it is about 30-90%. In some embodiments, it is about 30-80%. In some embodiments, it is about 30-70%. In some embodiments, it is about 40-90%. In some embodiments, it is about 40-80%. In some embodiments, it is about 40-70%.

[00659] Levels of oligonucleotides of a plurality in chirally controlled oligonucleotide compositions are controlled. In contrast, in non-chirally controlled (or stereorandom, racemic) oligonucleotide compositions (or preparations), levels of oligonucleotides are random and not controlled. In some embodiments, an enrichment relative to a substantially racemic preparation is a level described herein.

[00660] In some embodiments, a level as a percentage (e.g., a controlled level, a pre-determined level, an enrichment) is or is at least $(DS)^{nc}$, wherein DS (diastereopurity of an individual internucleotidic linkage) is 90%-100%, and nc is the number of chirally controlled internucleotidic linkages as described in the present disclosure (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more). In some embodiments, each chiral internucleotidic linkage is chirally controlled, and nc is the number of chiral internucleotidic linkage. In some embodiments, DS is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more. In some embodiments, DS is or is at least 90%. In some embodiments, DS is or is at least 91%. In some embodiments, DS is or is at least 92%. In some embodiments, DS is or is at least 93%. In some embodiments, DS is or is at least 94%. In some embodiments, DS is or is at least 95%. In some embodiments, DS is or is at least 96%. In some embodiments, DS is or is at least 97%. In some embodiments, DS is or is at least 98%.

In some embodiments, DS is or is at least 99%. In some embodiments, a level (e.g., a controlled level, a pre-determined level, an enrichment) is a percentage of all oligonucleotides in a composition that share the same constitution, wherein the percentage is or is at least $(DS)^{nc}$. For example, when DS is 99% and nc is 10, the percentage is or is at least 90% ($(99\%)^{10} \approx 0.90 = 90\%$). As appreciated by those skilled in the art, in a stereorandom preparation the percentage is typically about $1/2^{nc}$ - when nc is 10, the percentage is about $1/2^{10} \approx 0.001 = 0.1\%$. In some embodiments, an enrichment (e.g., relative to a substantially racemic preparation), a level, etc., is that at least about $(DS)^{nc}$ of all oligonucleotides in the composition, or all oligonucleotides in the composition that share the common base sequence of a plurality, or all oligonucleotides in the composition that share the common constitution of a plurality, are oligonucleotide of the plurality. In some embodiments, it is of all oligonucleotides in the composition. In some embodiments, it is of all oligonucleotides in the composition that share the common base sequence of a plurality. In some embodiments, it is of all oligonucleotides in the composition that share the common constitution of a plurality. In some embodiments, various forms (e.g., various salt forms) of an oligonucleotide may be properly considered to have the same constitution.

[00661] In some embodiments, oligonucleotides comprise one or more (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) chirally controlled chiral internucleotidic linkages the diastereomeric excess (d.e.) of whose linkage phosphorus is independently about or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%. In some embodiments, about or at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95% of all chiral internucleotidic linkages comprising a chiral linkage phosphorus are independently such a chirally controlled internucleotidic linkage. In some embodiments, about or at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95% of phosphorothioate internucleotidic linkages are independently such a chirally controlled internucleotidic linkage. In some embodiments, each phosphorothioate internucleotidic linkage is independently such a chirally controlled internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage comprising a chiral linkage phosphorus is independently such a chirally controlled internucleotidic linkage. In some embodiments, d.e. is about or at least about 80%. In some embodiments, d.e. is about or at least about 85%. In some embodiments, d.e. is about or at least about 90%. In some embodiments, d.e. is about or at least about 95%. In some embodiments, d.e. is about or at least about 96%. In some embodiments, d.e. is about or at least about 97%. In some embodiments, d.e. is about or at least about 98%.

[00662] In some embodiments, an oligonucleotide composition (also referred to as an oligonucleotide composition) is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common pattern of backbone linkages, and

the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the percentage of the oligonucleotides of the plurality within all oligonucleotides in the composition that share the common base sequence and pattern of backbone linkages is at least $(DS)^{nc}$, wherein DS is 90%-100%, and nc is the number of chirally controlled internucleotidic linkages.

[00663] In some embodiments, an oligonucleotide composition (also referred to as an oligonucleotide composition) is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence,

a common patter of backbone linkages, and

a common pattern of backbone chiral centers, which pattern comprises at least one *S*p,

wherein the percentage of the oligonucleotides of the plurality within all oligonucleotides in the composition that share the common base sequence and pattern of backbone linkages is at least $(DS)^{nc}$, wherein DS is 90%-100%, and nc is the number of chirally controlled internucleotidic linkages.

[00664] In some embodiments, level of a diastereopurity of a plurality of oligonucleotides in a composition can be determined as the product of the diastereopurity of each chirally controlled internucleotidic linkage in the oligonucleotides. In some embodiments, diastereopurity of an internucleotidic linkage connecting two nucleosides in an oligonucleotide (or nucleic acid) is represented by the diastereopurity of an internucleotidic linkage of a dimer connecting the same two nucleosides, wherein the dimer is prepared using comparable conditions, in some instances, identical synthetic cycle conditions (e.g., for the linkage between Nx and Ny in an oligonucleotide ….NxNy….., the dimer is NxNy).

[00665] In some embodiments, a chirally controlled oligonucleotide composition comprises two or more pluralities of oligonucleotides, wherein each plurality is independently a plurality of oligonucleotides as described herein (e.g., in various chirally controlled oligonucleotide compositions). For example, in some embodiments, each plurality independently shares a common base sequence, and the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages, and each plurality is independently enriched compared to stereorandom preparation of that plurality or each plurality is independently of a level as described herein. In some embodiments, at least two pluralities or each plurality independently targets a different adenosine. In some embodiments, at least two pluralities or each plurality independently targets a different transcript of the same or different nucleic acids. In some embodiments, at least two pluralities or each plurality independently targets transcripts of a different gene. Among other things, such compositions may be utilized to target two or more targets, in some embodiments, simultaneously and in the same system.

[00666] In some embodiments, all chiral internucleotidic linkages are chiral controlled, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, not all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition.

[00667] Oligonucleotides may comprise or consist of various patterns of backbone chiral centers (patterns of stereochemistry of chiral linkage phosphorus). Certain useful patterns of backbone chiral centers are

described in the present disclosure. In some embodiments, a plurality of oligonucleotides share a common pattern of backbone chiral centers, which is or comprises a pattern described in the present disclosure (e.g., as in "Linkage Phosphorus Stereochemistry and Patterns Thereof", a pattern of backbone chiral centers of a chirally controlled oligonucleotide in Table 1, etc.).

[00668] In some embodiments, a chirally controlled oligonucleotide composition is a chirally pure (or stereopure, stereochemically pure) oligonucleotide composition, wherein the oligonucleotide composition comprises a plurality of oligonucleotides, wherein the oligonucleotides are identical [including that each chiral element of the oligonucleotides, including each chiral linkage phosphorus, is independently defined (stereodefined)], and the composition does not contain other stereoisomers. A chirally pure (or stereopure, stereochemically pure) oligonucleotide composition of an oligonucleotide stereoisomer does not contain other stereoisomers (as appreciated by those skilled in the art, one or more unintended stereoisomers may exist as impurities).

[00669] Chirally controlled oligonucleotide compositions can demonstrate a number of advantages over stereorandom oligonucleotide compositions. Among other things, chirally controlled oligonucleotide compositions are more uniform than corresponding stereorandom oligonucleotide compositions with respect to oligonucleotide structures. By controlling stereochemistry, compositions of individual stereoisomers can be prepared and assessed, so that chirally controlled oligonucleotide composition of stereoisomers with desired properties and/or activities can be developed. In some embodiments, chirally controlled oligonucleotide compositions provides better delivery, stability, clearance, activity, selectivity, and/or toxicity profiles compared to, e.g., corresponding stereorandom oligonucleotide compositions. In some embodiments, chirally controlled oligonucleotide compositions provide better efficacy, fewer side effects, and/or more convenient and effective dosage regimens. Among other things, patterns of backbone chiral centers as described herein optionally combined with other structural features described herein, e.g., modifications of nucleobases, sugars, internucleotidic linkages, etc. can be utilized to provide to provide directed adenosine editing with high efficiency.

[00670] In some embodiments, an oligonucleotide composition comprises one or more internucleotidic linkages which are stereocontrolled (chirally controlled; in some embodiments, stereopure) and one or more internucleotidic linkages which are stereorandom. In some embodiments, an oligonucleotide composition comprises one or more internucleotidic linkages which are stereocontrolled (chirally controlled; in some embodiments, stereopure) and one or more internucleotidic linkages which are stereorandom.

[00671] In some embodiments, an oligonucleotide composition comprises one or more internucleotidic linkages which are stereocontrolled (e.g., chirally controlled or stereopure) and one or more internucleotidic linkages which are stereorandom. Such oligonucleotides may target various nucleic acids and may have various base sequences, and may provide efficient adenosine editing (e.g., conversion of A to I).

[00672] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition. In some embodiments, provided chirally controlled oligonucleotide compositions comprise a

plurality of oligonucleotides of the same constitution, and have one or more internucleotidic linkages. In some embodiments, a plurality of oligonucleotides, e.g., in a chirally controlled oligonucleotide composition, is a plurality of an oligonucleotide selected from Table 1 (and/or one or more of various salts forms thereof), wherein the oligonucleotide comprises at least one *R*p or *S*p linkage phosphorus in a chirally controlled internucleotidic linkage. In some embodiments, a plurality of oligonucleotides, e.g., in a chirally controlled oligonucleotide composition, is a plurality of an oligonucleotide selected from Table 1 (and/or one or more of various salts forms thereof), wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently chirally controlled (each phosphorothioate internucleotidic linkage is independently *R*p or *S*p). In some embodiments, an oligonucleotide composition, e.g., an oligonucleotide composition is a substantially pure preparation of a single oligonucleotide in that oligonucleotides in the composition that are not the single oligonucleotide are impurities from the preparation process of the single oligonucleotide, in some case, after certain purification procedures. In some embodiments, a single oligonucleotide is an oligonucleotide of Table 1, wherein each chiral internucleotidic linkage of the oligonucleotide is chirally controlled (e.g., indicated as S or R but not X in "Stereochemistry/Linkage").

[00673] In some embodiments, a chirally controlled oligonucleotide composition can have, relative to a corresponding stereorandom oligonucleotide composition, increased activity and/or stability, increased delivery, and/or decreased ability to elicit adverse effects such as complement, TLR9 activation, etc. In some embodiments, a stereorandom (non-chirally controlled) oligonucleotide composition differs from a chirally controlled oligonucleotide composition in that its corresponding plurality of oligonucleotides do not contain any chirally controlled internucleotidic linkages but the stereorandom oligonucleotide composition is otherwise identical to the chirally controlled oligonucleotide composition.

[00674] In some embodiments, the present disclosure pertains to a chirally controlled oligonucleotide composition which is capable of modulating level, activity or expression of a gene or a gene product thereof. In some embodiments, level, activity or expression of a gene or a gene product thereof is increased (e.g., through conversion of A to I to restore correct G to A mutations, to increase protein translation levels, to increase production of particular protein isoforms, to modulate splicing to increase levels of a particular splicing products and proteins encoded thereby, etc.), and in some embodiments, level, activity or expression of a gene or a gene product thereof is decreased (e.g., through conversion of A to I to create stop codon and/or alter codons, to decrease protein translation levels, to decrease production of particular protein isoforms, to modulate splicing to decrease levels of a particular splicing products and proteins encoded thereby, etc.), as compared to a reference condition (e.g., absence of oligonucleotides and/or compositions of the present disclosure, and/or presence of a reference oligonucleotide and/or oligonucleotide composition (e.g., oligonucleotides of the same base sequence but different modifications, stereorandom compositions of oligonucleotides of comparable structures (e.g., base sequence, modifications, etc.) but lack of stereochemical control, etc.).

[00675] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide

composition which is capable of increasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is, comprises, or comprises a span (e.g., at least 10 or 15 contiguous bases) of a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition which is capable of increasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is or comprises a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition which is capable of increasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa).

[00676] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition which is capable of decreasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is, comprises, or comprises a span (e.g., at least 10 or 15 contiguous bases) of a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition which is capable of decreasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is or comprises a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition which is capable of decreasing the level, activity or expression of a gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa).

[00677] In some embodiments, a provided chirally controlled oligonucleotide composition is a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotide. In some embodiments, a chirally controlled oligonucleotide composition is a chirally pure (or "stereochemically pure") oligonucleotide composition. In some embodiments, the present disclosure provides a chirally pure oligonucleotide composition of an oligonucleotide in Table 1, wherein each chiral internucleotidic linkage of the oligonucleotide is independently chirally controlled (*R*p or *S*p, e.g., can be determined from R or S but not X in "Stereochemistry/Linkage"). As one of ordinary skill in the art will understand, chemical selectivity rarely, if ever, achieves completeness (absolute 100%). In some embodiments, a chirally pure oligonucleotide composition comprises a plurality of oligonucleotides, wherein oligonucleotides of the plurality are structurally identical and all have the same structure (the same stereoisomeric form; in the context of oligonucleotide, typically the same diastereomeric form as typically multiple chiral centers exist in an oligonucleotide), and

the chirally pure oligonucleotide composition does not contain any other stereoisomers (in the context of oligonucleotide, typically diastereomers as typically multiple chiral centers exist in an oligonucleotide ; to the extent, e.g., achievable by stereoselective preparation). As appreciated by those skilled in the art, stereorandom (or "racemic", "non-chirally controlled") oligonucleotide compositions are random mixtures of many stereoisomers (e.g., 2^n diastereoisomers wherein n is the number of chiral linkage phosphorus for oligonucleotides in which other chiral centers (e.g., carbon chiral centers in sugars) are chirally controlled each independently existing in one configuration and only chiral linkage phosphorus centers are not chirally controlled).

[00678] Certain data showing properties and/or activities of chirally controlled oligonucleotide composition, e.g., chirally controlled oligonucleotide composition in modulating level, activity and/or expression of target genes and/or products thereof, are shown in, for example, the Examples of this disclosure.

[00679] In some embodiments, the present disclosure provides an oligonucleotide composition comprising oligonucleotides that comprise at least one chiral linkage phosphorus. In some embodiments, the present disclosure provides an oligonucleotide composition comprising oligonucleotides that comprise at least one chiral linkage phosphorus. In some embodiments, the present disclosure provides an oligonucleotide composition in which the oligonucleotides comprise a chirally controlled phosphorothioate internucleotidic linkage, wherein the linkage phosphorus has a *R*p configuration. In some embodiments, the present disclosure provides an oligonucleotide composition in which the oligonucleotides comprise a chirally controlled phosphorothioate internucleotidic linkage, wherein the linkage phosphorus has a *S*p configuration. In some embodiments, the present disclosure provides an oligonucleotide composition in which the oligonucleotides comprise a chirally controlled phosphorothioate internucleotidic linkage, wherein the linkage phosphorus has a *R*p configuration and the linkage phosphorus has a *S*p configuration. In some embodiments, such oligonucleotide compositions are chirally controlled, and the *R*p and/or *S*p internucleotidic linkages are independently chirally controlled internucleotidic linkages.

[00680] In some embodiments, compared to reference oligonucleotides or oligonucleotide compositions, provided oligonucleotides or oligonucleotide compositions (e.g., chirally controlled oligonucleotide compositions) are surprisingly effective. In some embodiments, desired biological effects (e.g., as measured by increased (if increase is desired) and/or decreased (if decrease is desired) levels of mRNA, proteins, etc. whose levels are targeted for increase) can be enhanced by more than 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, or 100 fold (e.g., as measured by levels of desired mRNA, proteins, etc.). In some embodiments, a change is measured by increase of desired mRNA and/or protein levels, or decrease of undesired mRNA and/or protein levels, compared to a reference condition. In some embodiments, a change is measured by increase of a desired mRNA and/or protein level compared to a reference condition. In some embodiments, a change is measured by decrease of an undesired mRNA and/or level compared to a reference condition. In some embodiments, a reference condition is absence of provided oligonucleotides or oligonucleotide compositions, and or presence of reference oligonucleotides or oligonucleotide compositions, respectively. In some

embodiments, a reference oligonucleotide shares the same base sequence, but different nucleobase modifications, sugar modifications, internucleotidic linkages modifications, and/or linkage phosphorus stereochemistry. In some embodiments, a reference oligonucleotide composition is a composition of oligonucleotides of the same base sequence, but different nucleobase modifications, sugar modifications, internucleotidic linkages modifications, and/or linkage phosphorus stereochemistry. In some embodiments, a reference composition for a chirally controlled oligonucleotide composition is a corresponding stereorandom composition of oligonucleotides having the same base sequence, nucleobase modifications, sugar modifications, and/or internucleotidic linkages modifications (but lack of and/or low levels of linkage phosphorus stereochemistry control), or having the same constitution.

[00681] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein the linkage phosphorus of at least one chirally controlled internucleotidic linkage is *S*p. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein the majority of linkage phosphorus of chirally controlled internucleotidic linkages are *S*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all chirally controlled internucleotidic linkages (or of all chiral internucleotidic linkages, or of all internucleotidic linkages) are *S*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all chirally controlled phosphorothioate internucleotidic linkages are *S*p. In some embodiments, no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of phosphorothioate internucleotidic linkages are non-chirally controlled or are chirally controlled and *R*p. In some embodiments, no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of phosphorothioate internucleotidic linkages are are chirally controlled and *R*p. In some embodiments, it is no more than 1. In some embodiments, it is no more than 2. In some embodiments, it is no more than 3. In some embodiments, it is no more than 4. In some embodiments, it is no more than 5. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein the majority of chiral internucleotidic linkages are chirally controlled and are *S*p at their linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein each chiral internucleotidic linkage is chirally controlled and each chiral linkage phosphorus is *S*p. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., chirally controlled oligonucleotide composition, wherein at least one chirally controlled internucleotidic linkage has a *R*p linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein at least one chirally controlled internucleotidic linkage comprises a *R*p linkage phosphorus and at least one chirally controlled internucleotidic linkage comprises a *S*p linkage phosphorus.

[00682] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide

composition, wherein at least two chirally controlled internucleotidic linkages have different linkage phosphorus stereochemistry and/or different P-modifications relative to one another, wherein a P-modification is a modification at a linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, wherein at least two chirally controlled internucleotidic linkages have different stereochemistry relative to one another, and the pattern of the backbone chiral centers of the oligonucleotides is characterized by a repeating pattern of alternating stereochemistry.

[00683] In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a natural phosphate linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a phosphorothioate internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a natural phosphate linkage and a phosphorothioate internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a phosphorothioate triester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a natural phosphate linkage and a phosphorothioate triester internucleotidic linkage. In certain embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein with in each of the oligonucleotides at least two individual internucleotidic linkages have different P-modifications relative to one another, and each of the oligonucleotide comprises a phosphorothioate internucleotidic linkage and a phosphorothioate triester internucleotidic linkage.

[00684] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, comprising a plurality of oligonucleotides which share a common base sequence that is the base sequence of an oligonucleotide disclosed herein, wherein at least one internucleotidic linkage is chirally controlled.

Linkage Phosphorus Stereochemistry and Pattern of Backbone Chiral Centers

[00685] Among other things, the present disclosure provides various oligonucleotide compositions. In some embodiments, the present disclosure provides oligonucleotide compositions of oligonucleotides described herein. In some embodiments, an oligonucleotide composition comprises a plurality of oligonucleotides described in the present disclosure. In some embodiments, an oligonucleotide composition is chirally controlled. In some embodiments, an oligonucleotide composition is not chirally controlled (stereorandom).

[00686] In contrast to natural phosphate linkages, linkage phosphorus of chiral modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are chiral. Among other things, the present disclosure provides technologies (e.g., oligonucleotides, compositions, methods, etc.) comprising control of stereochemistry of chiral linkage phosphorus in chiral internucleotidic linkages. In some embodiments, as demonstrated herein, control of stereochemistry can provide improved properties and/or activities, including desired stability, reduced toxicity, improved modification of target nucleic acids, improved modulation of levels of transcripts and/or products (e.g., mRNA, proteins, etc.) encoded thereof, etc. In some embodiments, the present disclosure provides useful patterns of backbone chiral centers for oligonucleotides and/or regions thereof, which pattern includes a combination of stereochemistry of each chiral linkage phosphorus (*Rp* or *Sp*) of chiral linkage phosphorus, indication of each achiral linkage phosphorus (Op, if any), etc. from 5' to 3'. Certain patterns are provided in various Tables (e.g., Stereochemistry/Linkage as examples; such patterns can be applied to various oligonucleotides with various base sequences and modifications (e.g., those described herein including patterns thereof).

[00687] Useful patterns of backbone chiral centers, e.g., those for oligonucleotides, first domains, second domains, first subdomains, second subdomains, third subdomains, etc., are extensively described herein. For example, in some embodiments, high levels of *Sp* internucleotidic linkages of oligonucleotides or of one or more portions thereof (e.g., first domains, second domains, first subdomains, second subdomains, and/or third subdomains, and/or 5'-end portions and/or 3'-end portions therein) provide high stability and/or activities. In some embodiments, first domains contain high levels of *Sp* internucleotidic linkages. In some embodiments, second domains contain high levels of *Sp* internucleotidic linkages (in numbers and/or percentages, relative to natural phosphate linkages and/or *Rp* internucleotidic linkages). In some embodiments, first subdomains contain high levels of *Sp* internucleotidic linkages. In some embodiments, second subdomains contain high levels of *Sp* internucleotidic linkages. In some embodiments, third subdomains contain high levels of *Sp* internucleotidic linkages. In some embodiments, as demonstrated herein *Rp* internucleotidic linkages can be utilized in various locations and/or portions. For example, in some embodiments, first domains contain one or more or high levels of *Rp* internucleotidic linkages, and in some embodiments, second subdomains contain one or more or high levels of *Rp* internucleotidic linkages.

[00688] In some embodiments, a number of linkage phosphorus in chirally controlled internucleotidic

linkages are *S*p. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of chirally controlled internucleotidic linkages have *S*p linkage phosphorus. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of all chiral internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of all internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of all phosphorothioate internucleotidic linkages have *S*p linkage phosphorus. In some embodiments, the percentage is at least 20%. In some embodiments, the percentage is at least 30%. In some embodiments, the percentage is at least 40%. In some embodiments, the percentage is at least 50%. In some embodiments, the percentage is at least 60%. In some embodiments, the percentage is at least 65%. In some embodiments, the percentage is at least 70%. In some embodiments, the percentage is at least 75%. In some embodiments, the percentage is at least 80%. In some embodiments, the percentage is at least 90%. In some embodiments, the percentage is at least 95%. In some embodiments, all chirally controlled internucleotidic linkages have *S*p linkage phosphorus. In some embodiments, all chirally controlled phosphorothioate internucleotidic linkages have *S*p linkage phosphorus. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 5 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 6 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 7 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 8 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 9 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 10 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 11 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 12 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 13 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 14 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 15 internucleotidic linkages are chirally controlled internucleotidic linkages having *S*p linkage phosphorus. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 internucleotidic linkages are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,

41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 internucleotidic linkages are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, one and no more than one internucleotidic linkage in an oligonucleotide is a chirally controlled internucleotidic linkage having *R*p linkage phosphorus. In some embodiments, 2 and no more than 2 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 3 and no more than 3 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 4 and no more than 4 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 5 and no more than 5 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus.

[00689] In some embodiments, all, essentially all or most of the internucleotidic linkages in an oligonucleotide or a portion thereof are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages in an oligonucleotide) except for one or a minority of internucleotidic linkages (e.g., 1, 2, 3, 4, or 5, and/or less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages in an oligonucleotide) being in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a first domain are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in a first domain). In some embodiments, each internucleotidic linkage in a first domain is a phosphorothioate in the *S*p configuration. In some embodiments, each internucleotidic linkage in the a domain is a phosphorothioate in the *S*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a second domain are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in a second domain). In some embodiments, each internucleotidic linkage in a second domain is a phosphorothioate in the *S*p configuration. In some embodiments, each internucleotidic linkage in a second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a subdomain of a second domain are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or

more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in a first subdomain of a second domain). In some embodiments, each internucleotidic linkage in a first subdomain of a second domain is a phosphorothioate in the *S*p configuration. In some embodiments, each internucleotidic linkage in a first subdomain of second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a the second subdomain of a second domain are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in a second subdomain of a second domain) except for one or a minority of internucleotidic linkages being in the *R*p configuration. In some embodiments, each internucleotidic linkage in a second subdomain of a second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, each internucleotidic linkage in a second subdomain of a second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a the third subdomain of the second domain are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in a third subdomain of a second domain. In some embodiments, each internucleotidic linkage in a third subdomain of a second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, each internucleotidic linkage in a third subdomain of a second domain is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration.

[00690] In some embodiments, an oligonucleotide comprises one or more *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises one and no more than one *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises five or more *R*p internucleotidic linkages. In some embodiments, about 5%-50% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 5%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, certain portions (e.g., domains, subdomains, etc.) may contain relatively more (in numbers and/or percentages) *R*p internucleotidic linkages, e.g., second subdomains.

[00691] In some embodiments, an oligonucleotide comprises one or more *R*p phosphorothioate internucleotidic linkages at one or more positions, e.g., -1, -2, +1, +2, +7, +8, etc. In some embodiments, an internucleotidic linkage at position -1 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -2 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +1 is a *R*p phosphorothioate internucleotidic linkage. In

some embodiments, an internucleotidic linkage at position +2 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, two or three internucleotidic linkages at positions -1, -2, +1, and +2 *R*p phosphorothioate internucleotidic linkages. In some embodiments, the positions are -1 and -2. In some embodiments, the positions are +1 and +2. In some embodiments, the positions are -1 and +1. In some embodiments, the positions are -1, +1 and +2. In some embodiments, the positions are -1, -2 and +1. In some embodiments, one and only one internucleotidic linkage is *R*p phosphorothioate internucleotidic linkage. In some embodiments, one and only one internucleotidic linkage is *R*p phosphorothioate internucleotidic linkage and is at position +2, +1, 1 or 2. In some embodiments, a position is +1. In some embodiments, a position is +2. In some embodiments, a position is -1. In some embodiments, a position is -2. In some embodiments, it is observed that utilization of *R*p internucleotidic linkages may improve editing efficiency by ADAR1 (p110 and/or p150) and/or ADAR2. In some embodiments, improvements of editing by ADAR1 (p110 and/or p150) are more than those by ADAR2 (no or less improvements or less editing compared to absence of *R*p).

[00692] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition wherein the composition comprises a non-random or controlled level of a plurality of oligonucleotides, wherein oligonucleotides of the plurality share a common base sequence, and share the same configuration of linkage phosphorus independently at 1-60, 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more chiral internucleotidic linkages.

[00693] In some embodiments, provided oligonucleotides comprise 2-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotide compositions comprise 5-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotide compositions comprise 10-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotide compositions comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more chirally controlled internucleotidic linkages.

[00694] In some embodiments, about 1-100% of all internucleotidic linkages are chirally controlled internucleotidic linkages. In some embodiments, about 1-100% of all chiral internucleotidic linkages are chirally controlled internucleotidic linkages. In some embodiments, a percentage is about 5%-100%. In some embodiments, a percentage is at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%. In some embodiments, a percentage is about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%.

[00695] In some embodiments, an internucleotidic linkage in the *S*p configuration (having a *S*p linkage phosphorus) is a phosphorothioate internucleotidic linkage. In some embodiments, an achiral internucleotidic linkage is a natural phosphate linkage. In some embodiments, an internucleotidic linkage in the *R*p configuration (having a *R*p linkage phosphorus) is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage in the *S*p configuration is a phosphorothioate internucleotidic

linkage. In some embodiments, each achiral internucleotidic linkage is a natural phosphate linkage. In some embodiments, each internucleotidic linkage in the *R*p configuration is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage in the *S*p configuration is a phosphorothioate internucleotidic linkage, each achiral internucleotidic linkage is a natural phosphate linkage, and each internucleotidic linkage in the *R*p configuration is a phosphorothioate internucleotidic linkage.

[00696] In some embodiments, provided oligonucleotides in chirally controlled oligonucleotide compositions each comprise different types of internucleotidic linkages. In some embodiments, provided oligonucleotides comprise at least one natural phosphate linkage and at least one modified internucleotidic linkage. In some embodiments, provided oligonucleotides comprise at least one natural phosphate linkage and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is independently a chiral internucleotidic linkage and is independently chirally controlled.

[00697] In some embodiments, oligonucleotides in a chirally controlled oligonucleotide composition each comprise at least two internucleotidic linkages that have different stereochemistry and/or different P-modifications relative to one another. In some embodiments, at least two internucleotidic linkages have different stereochemistry relative to one another. In some embodiments, oligonucleotides each comprise a pattern of backbone chiral centers comprising alternating linkage phosphorus stereochemistry.

[00698] In some embodiments, a phosphorothioate triester linkage comprises a chiral auxiliary, which, for example, is used to control the stereoselectivity of a reaction, e.g., a coupling reaction in an oligonucleotide synthesis cycle. In some embodiments, a phosphorothioate triester linkage does not comprise a chiral auxiliary. In some embodiments, a phosphorothioate triester linkage is intentionally maintained until and/or during the administration of the oligonucleotide composition to a subject.

[00699] In some embodiments, oligonucleotides are linked to a solid support. In some embodiments, a solid support is a support for oligonucleotide synthesis. In some embodiments, a solid support comprises glass. In some embodiments, a solid support is CPG (controlled pore glass). In some embodiments, a solid support is polymer. In some embodiments, a solid support is polystyrene. In some embodiments, the solid support is Highly Crosslinked Polystyrene (HCP). In some embodiments, the solid support is hybrid support of Controlled Pore Glass (CPG) and Highly Cross-linked Polystyrene (HCP). In some embodiments, a solid support is a metal foam. In some embodiments, a solid support is a resin. In some embodiments, oligonucleotides are cleaved from a solid support.

[00700] In some embodiments, purity, particularly stereochemical purity, and particularly diastereomeric purity of many oligonucleotides and compositions thereof wherein all other chiral centers in the oligonucleotides but the chiral linkage phosphorus centers have been stereodefined (e.g., carbon chiral centers

in the sugars, which are defined in, *e.g.*, phosphoramidites for oligonucleotide synthesis), can be controlled by stereoselectivity (as appreciated by those skilled in this art, diastereoselectivity in many cases of oligonucleotide synthesis wherein the oligonucleotide comprise more than one chiral centers) at chiral linkage phosphorus in coupling steps when forming chiral internucleotidic linkages. In some embodiments, a coupling step has a stereoselectivity (diastereoselectivity when there are other chiral centers) of 60% at the linkage phosphorus. After such a coupling step, the new internucleotidic linkage formed may be referred to have a 60% stereochemical purity (for oligonucleotides, typically diastereomeric purity in view of the existence of other chiral centers). In some embodiments, each coupling step independently has a stereoselectivity of at least 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%. In some embodiments, a chirally controlled internucleotidic linkage is typically formed with a stereoselectivity of at least 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99.5% or virtually 100% (in some embodiments, at least 85%; in some embodiments, at least 87%; in some embodiments, at least 90%; in some embodiments, at least 95%; in some embodiments, at least 96%; in some embodiments, at least 97%; in some embodiments, at least 98%; in some embodiments, at least 99%). In some embodiments, a stereoselectivity is at least 85%. In some embodiments, a stereoselectivity is at least 87%. In some embodiments, a stereoselectivity is at least 90%. In some embodiments, each coupling step independently has a stereoselectivity of virtually 100%.

[00701] In some embodiments, stereopurity of a chiral center, e.g., a chiral linkage phosphorus, in a composition is at least 60%, 70%, 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%. In some embodiments, a stereopurity is at least 80%. In some embodiments, a stereopurity is at least 85%. In some embodiments, a stereopurity is at least 87%. In some embodiments, a stereopurity is at least 90%. In some embodiments, a stereopurity is virtually 100%. In some embodiments, each chirally controlled internucleotidic linkage independently has a stereochemical purity (typically diastereomeric purity for oligonucleotides with multiple chiral centers) of at least 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99.5% or virtually 100% (in some embodiments, at least 85%; in some embodiments, at least 87%; in some embodiments, at least 90%; in some embodiments, at least 95%; in some embodiments, at least 96%; in some embodiments, at least 97%; in some embodiments, at least 98%; in some embodiments, at least 99%) at its chiral linkage phosphorus. In some embodiments, a chirally controlled internucleotidic linkage has a stereochemical purity of at least 90%. In some embodiments, a majority of chirally controlled internucleotidic linkages independently have a stereochemical purity of at least 90%. In some embodiments, each chirally controlled internucleotidic linkage independently has a stereochemical purity of at least 90%. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all chirally controlled internucleotidic linkages are *S*p. In some embodiments, at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all chirally controlled phosphorothioate internucleotidic linkages are *S*p. In some embodiments, at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or all phosphorothioate internucleotidic linkages are

chirally controlled and are *S*p.

[00702] Stereoselectivity and stereopurity may be assessed by various technologies. In some embodiments, stereoselectivity and/or stereopurity is virtually 100% in that when a composition is analyzed by an analytical method (e.g., NMR, HPLC, etc.), virtually all detectable stereoisomers has the intended stereochemistry.

[00703] In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 couplings of a monomer (as appreciated by those skilled in the art in many embodiments a phosphoramidite for oligonucleotide synthesis) independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90% [for oligonucleotide synthesis, typically diastereoselectivity with respect to formed linkage phosphorus chiral center(s)].

[00704] In some embodiments, in stereorandom (or racemic) preparations (or stereorandom/non-chirally controlled oligonucleotide compositions), at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 chiral internucleotidic linkages of the oligonucleotides independently have a stereochemical purity (typically diastereomeric purity for oligonucleotides comprising multiple chiral centers) less than about 60%, 65%, 70%, 75%, 80%, or 85% with respect to chiral linkage phosphorus of the internucleotidic linkage(s). In some embodiments, a stereochemistry purity (stereopurity) is less than about 60%. In some embodiments, a stereochemistry purity (stereopurity) is less than about 65%. In some embodiments, a stereochemistry purity (stereopurity) is less than about 70%. In some embodiments, a stereochemistry purity (stereopurity) is less than about 75%. In some embodiments, a stereochemistry purity (stereopurity) is less than about 80%.

[00705] In some embodiments, compounds of the present disclosure (e.g., oligonucleotides, chiral auxiliaries, etc.) comprise multiple chiral elements (e.g., multiple carbon and/or phosphorus (e.g., linkage phosphorus of chiral internucleotidic linkages) chiral centers). In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral elements of a provided compound (e.g., an oligonucleotide) each independently have a diastereomeric purity as described herein. In some embodiments, a diastereomeric purity is at least 85%. In some embodiments, a diastereomeric purity is at least 86%. In some embodiments, a diastereomeric purity is at least 87%. In some embodiments, a diastereomeric purity is at least 88%. In some embodiments, a diastereomeric purity is at least 89%. In some embodiments, a diastereomeric purity is at least 90%. In some embodiments, a diastereomeric purity is at least 91%. In some embodiments, a diastereomeric purity is at least 92%. In some embodiments, a diastereomeric purity is at least 93%. In some embodiments, a diastereomeric purity is at least 94%. In some embodiments, a diastereomeric purity is at least 95%. In some embodiments, a diastereomeric purity is at least 96%. In some embodiments, a diastereomeric purity is at least 97%. In some embodiments, a diastereomeric purity is at least 98%. In some embodiments, a diastereomeric purity is at least 99%.

[00706] As understood by a person having ordinary skill in the art, in some embodiments, diastereoselectivity of a coupling or diastereomeric purity of a chiral linkage phosphorus center can be assessed through the diastereoselectivity of a dimer formation or diastereomeric purity of a dimer prepared under the

same or comparable conditions, wherein the dimer has the same 5'- and 3'-nucleosides and internucleotidic linkage.

[00707] Various technologies can be utilized for identifying or confirming stereochemistry of chiral elements (e.g., configuration of chiral linkage phosphorus) and/or patterns of backbone chiral centers, and/or for assessing stereoselectivity (e.g., diastereoselectivity of couple steps in oligonucleotide synthesis) and/or stereochemical purity (e.g., diastereomeric purity of internucleotidic linkages, compounds (e.g., oligonucleotides), etc.). Example technologies include NMR [e.g., 1D (one-dimensional) and/or 2D (two-dimensional) ^{1}H-^{31}P HETCOR (heteronuclear correlation spectroscopy)], HPLC, RP-HPLC, mass spectrometry, LC-MS, and cleavage of internucleotidic linkages by stereospecific nucleases, etc., which may be utilized individually or in combination. Example useful nucleases include benzonase, micrococcal nuclease, and svPDE (snake venom phosphodiesterase), which are specific for certain internucleotidic linkages with *Rp* linkage phosphorus (e.g., a *Rp* phosphorothioate linkage); and nuclease P1, mung bean nuclease, and nuclease S1, which are specific for internucleotidic linkages with *S*p linkage phosphorus (e.g., a *S*p phosphorothioate linkage). Without wishing to be bound by any particular theory, the present disclosure notes that, in at least some cases, cleavage of oligonucleotides by a particular nuclease may be impacted by structural elements, e.g., chemical modifications (e.g., 2'-modifications of a sugars), base sequences, or stereochemical contexts. For example, it is observed that in some cases, benzonase and micrococcal nuclease, which are specific for internucleotidic linkages with *Rp* linkage phosphorus, were unable to cleave an isolated *Rp* phosphorothioate internucleotidic linkage flanked by *S*p phosphorothioate internucleotidic linkages.

[00708] In some embodiments, oligonucleotides sharing a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers share a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotide compositions sharing a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers share a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

[00709] In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides capable of directing deamination of a target adenosine in a target nucleic acid, wherein oligonucleotides of the plurality are of a particular oligonucleotide type, which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, for oligonucleotides of the particular oligonucleotide type.

[00710] In some embodiments, a plurality of oligonucleotides or oligonucleotides of a particular oligonucleotide type in a provided oligonucleotide composition are oligonucleotides. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence;

a common pattern of backbone linkages; and

the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality.

[00711] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein the oligonucleotides share:

a common base sequence;

a common pattern of backbone linkages; and

a common pattern of backbone chiral centers, which composition is a substantially pure preparation of a single oligonucleotide in that at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 93%, 95%, 96%, 97%, 98%, or 99% of the oligonucleotides in the composition have the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone chiral centers.

[00712] In some embodiments, an oligonucleotide composition type is further defined by: 4) additional chemical moiety, if any.

[00713] In some embodiments, the percentage is at least about 10%. In some embodiments, the percentage is at least about 20%. In some embodiments, the percentage is at least about 30%. In some embodiments, the percentage is at least about 40%. In some embodiments, the percentage is at least about 50%. In some embodiments, the percentage is at least about 60%. In some embodiments, the percentage is at least about 70%. In some embodiments, the percentage is at least about 75%. In some embodiments, the percentage is at least about 80%. In some embodiments, the percentage is at least about 85%. In some embodiments, the percentage is at least about 90%. In some embodiments, the percentage is at least about 91%. In some embodiments, the percentage is at least about 92%. In some embodiments, the percentage is at least about 93%. In some embodiments, the percentage is at least about 94%. In some embodiments, the percentage is at least about 95%. In some embodiments, the percentage is at least about 96%. In some embodiments, the percentage is at least about 97%. In some embodiments, the percentage is at least about 98%. In some embodiments, the percentage is at least about 99%. In some embodiments, the percentage is or is greater than $(DS)^{nc}$, wherein DS and nc are each independently as described in the present disclosure.

[00714] In some embodiments, a plurality of oligonucleotides share the same constitution. In some embodiments, a plurality of oligonucleotides are identical (the same stereoisomer). In some embodiments, a chirally controlled oligonucleotide composition is a stereopure oligonucleotide composition wherein oligonucleotides of the plurality are identical (the same stereoisomer), and the composition does not contain any other stereoisomers. Those skilled in the art will appreciate that one or more other stereoisomers may exist as impurities as processes, selectivities, purifications, etc. may not achieve completeness.

[00715] In some embodiments, a provided composition is characterized in that when it is contacted with a target nucleic acid [e.g., a transcript (e.g., pre-mRNA, mature mRNA, other types of RNA, etc. that hybridizes with oligonucleotides of the composition)], levels of the target nucleic acid and/or a product encoded thereby is reduced compared to that observed under a reference condition. In some embodiments, levels of a nucleic acid and/or a product thereof, which nucleic acid is a product of an A to I edition of a target nucleic acid, is increased. In some embodiments, a reference condition is selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. In some embodiments, a reference condition is absence of the composition. In some embodiments, a reference condition is presence of a reference composition. In some embodiments, a reference composition is a composition whose oligonucleotides do not hybridize with the target nucleic acid. In some embodiments, a reference composition is a composition whose oligonucleotides do not comprise a sequence that is sufficiently complementary to the target nucleic acid. In some embodiments, a reference composition is a composition whose oligonucleotides share the same base sequence but do not share the same nucleobase, sugar and/or internucleotidic linkage modifications. In some embodiments, a provided composition is a chirally controlled oligonucleotide composition and a reference composition is a non-chirally controlled oligonucleotide composition which is otherwise identical but is not chirally controlled (e.g., a racemic preparation of oligonucleotides of the same constitution as oligonucleotides of a plurality in the chirally controlled oligonucleotide composition).

[00716] In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides capable of directing deamination of a target adenosine in a target nucleic acid, wherein the oligonucleotides share:

a common base sequence,

a common pattern of backbone linkages, and

the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality,

the oligonucleotide composition being characterized in that, when it is contacted with a target sequence, deamination of the target adenosine in the target nucleic acid is improved relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

[00717] As appreciated by those skilled in the art, deamination of a target adenosine can be assessed using various technologies. In some embodiments, a technology is sequencing, wherein a deaminated adenosine is detected as G or I. In some embodiments, deamination is assessed by levels of a product (e.g., RNA, protein (e.g., encoded by a sequence wherein a target A is replaced with I but is otherwise identical to a target nucleic acid), etc.).

[00718] As demonstrated herein, oligonucleotide structural elements (e.g., sugar modifications, backbone

linkages, backbone chiral centers, backbone phosphorus modifications, patterns thereof, etc.) and combinations thereof can provide surprisingly improved properties and/or bioactivities.

[00719] In some embodiments, an oligonucleotide composition is a substantially pure preparation of a single oligonucleotide stereoisomer in that oligonucleotides in the composition that are of the same constitution but are not of the stereoisomer are impurities from the preparation process of said oligonucleotide stereoisomer, in some case, after certain purification procedures.

[00720] In some embodiments, the present disclosure provides oligonucleotides and oligonucleotide compositions that are chirally controlled, and in some embodiments, stereopure. For instance, in some embodiments, a provided composition contains non-random or controlled levels of one or more individual oligonucleotide types. In some embodiments, oligonucleotides of the same oligonucleotide type are identical.

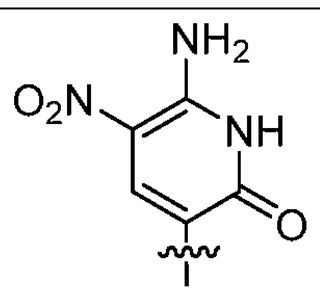
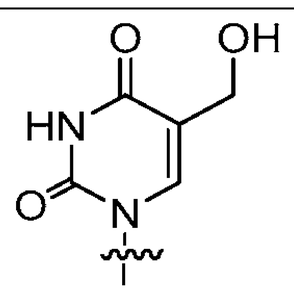
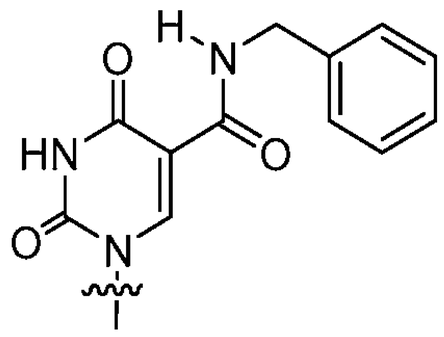
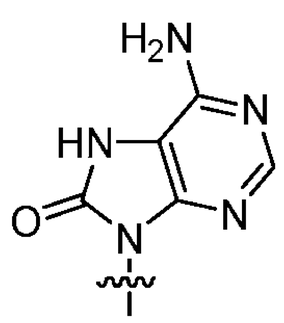
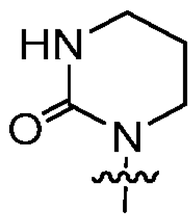
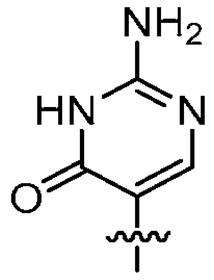
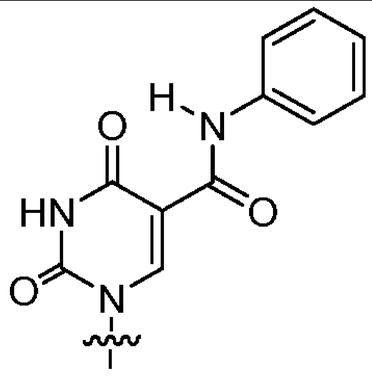
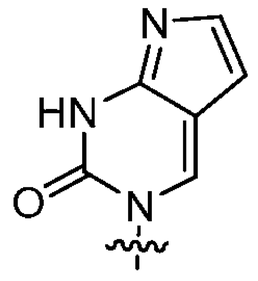
Nucleobases

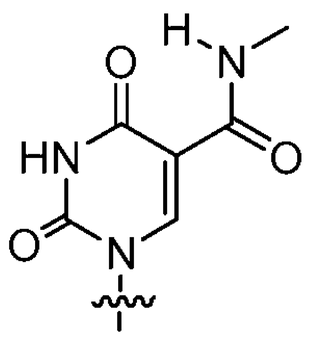
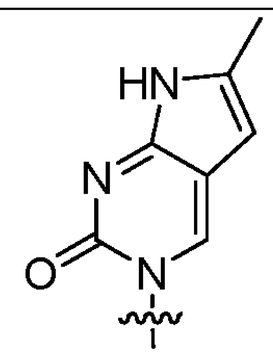
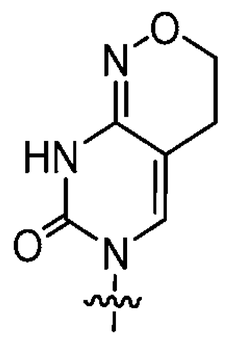
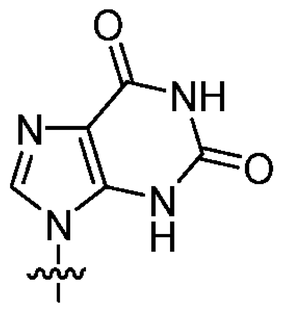
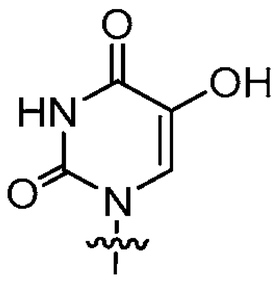
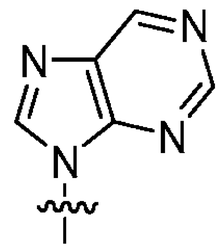
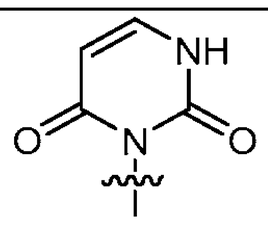
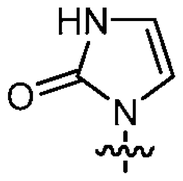
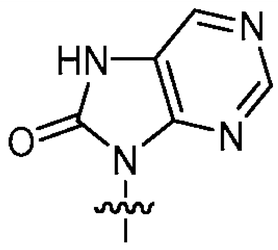
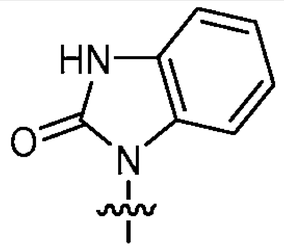
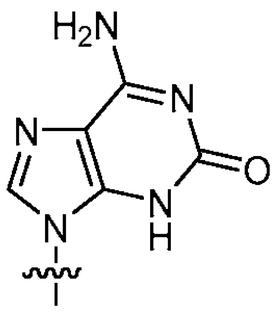
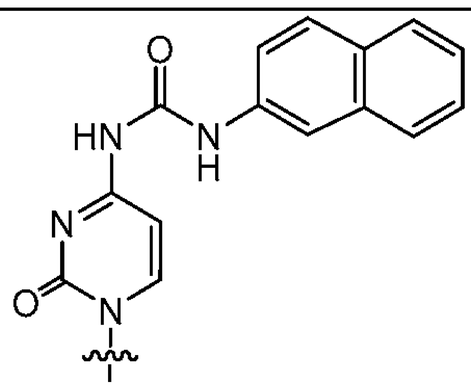
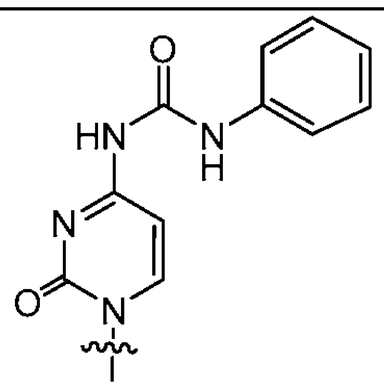
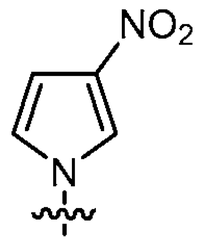
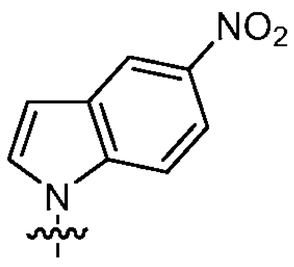
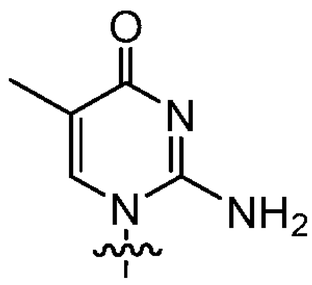
[00721] Various nucleobases may be utilized in provided oligonucleotides in accordance with the present disclosure. In some embodiments, a nucleobase is a natural nucleobase, the most commonly occurring ones being A, T, C, G and U. In some embodiments, a nucleobase is a modified nucleobase in that it is not A, T, C, G or U. In some embodiments, a nucleobase is optionally substituted A, T, C, G or U, or a substituted tautomer of A T, C, G or U. In some embodiments, a nucleobase is optionally substituted A, T, C, G or U, e.g., 5mC, 5-hydroxymethyl C, etc. In some embodiments, a nucleobase is alkyl-substituted A, T, C, G or U. In some embodiments, a nucleobase is A. In some embodiments, a nucleobase is T. In some embodiments, a nucleobase is C. In some embodiments, a nucleobase is G. In some embodiments, a nucleobase is U. In some embodiments, a nucleobase is 5mC. In some embodiments, a nucleobase is substituted A, T, C, G or U. In some embodiments, a nucleobase is a substituted tautomer of A, T, C, G or U. In some embodiments, substitution protects certain functional groups in nucleobases to minimize undesired reactions during oligonucleotide synthesis. Suitable technologies for nucleobase protection in oligonucleotide synthesis are widely known in the art and may be utilized in accordance with the present disclosure. In some embodiments, modified nucleobases improves properties and/or activities of oligonucleotides. For example, in many cases, 5mC may be utilized in place of C to modulate certain undesired biological effects, e.g., immune responses. In some embodiments, when determining sequence identity, a substituted nucleobase having the same hydrogen-bonding pattern is treated as the same as the unsubstituted nucleobase, e.g., 5mC may be treated the same as C [e.g., an oligonucleotide having 5mC in place of C (e.g., AT5mCG) is considered to have the same base sequence as an oligonucleotide having C at the corresponding location(s) (e.g., ATCG)]. In some embodiments, a nucleobase is or comprise an optionally substituted ring having at least one nitrogen atom. In some embodiments, a nucleobase comprise Ring BA as described herein, wherein at least one monocyclic ring of Ring BA comprise a nitrogen ring atom.

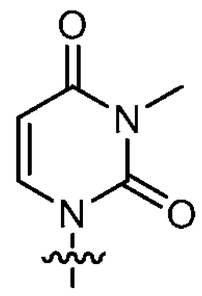
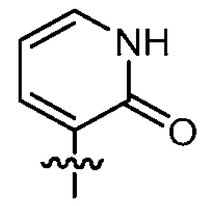
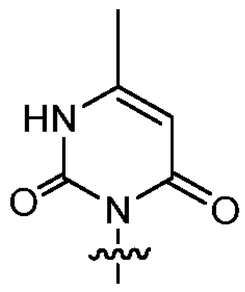
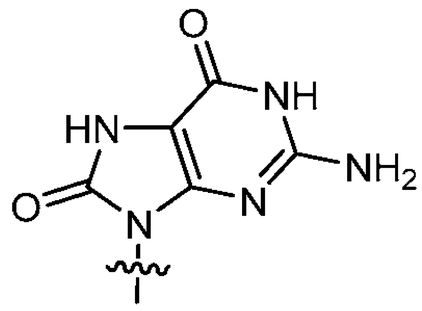
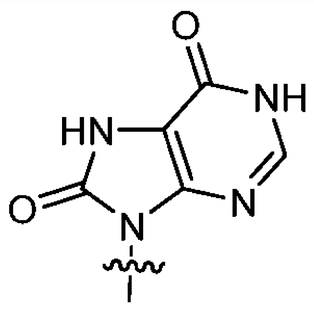
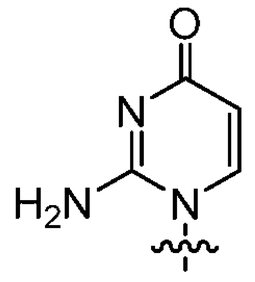
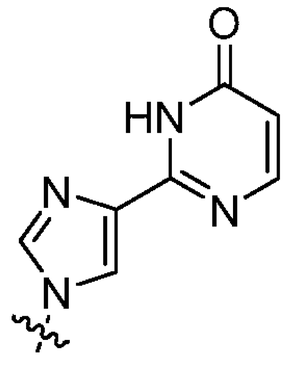
[00722] In some embodiments, an oligonucleotide comprises one or more A, T, C, G or U. In some embodiments, an oligonucleotide comprises one or more optionally substituted A, T, C, G or U. In some

embodiments, an oligonucleotide comprises one or more 5-methylcytidine, 5-hydroxymethylcytidine, 5-formylcytosine, or 5-carboxylcytosine. In some embodiments, an oligonucleotide comprises one or more 5-methylcytidine. In some embodiments, each nucleobase in an oligonucleotide is selected from the group consisting of optionally substituted A, T, C, G and U, and optionally substituted tautomers of A, T, C, G and U. In some embodiments, each nucleobase in an oligonucleotide is optionally protected A, T, C, G and U. In some embodiments, each nucleobase in an oligonucleotide is optionally substituted A, T, C, G or U. In some embodiments, each nucleobase in an oligonucleotide is selected from the group consisting of A, T, C, G, U, and 5mC.

[00723] As demonstrated herein, utilization of certain nucleobases at certain locations (e.g., in a nucleoside opposite to a target adenosine and/or its adjacent nucleoside(s)) can provide oligonucleotides with improved properties and/or activities (e.g., adenosine editing to I). In some embodiments, a useful nucleobase is or comprises Ring BA as described herein. In some embodiments, a nucleobase in a nucleoside is or comprises Ring BA which has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected. In some embodiments, a nucleobase is optionally substituted or protected, or optionally substituted or protected tautomer of:

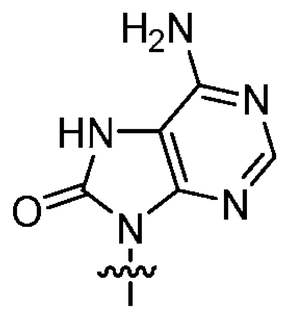
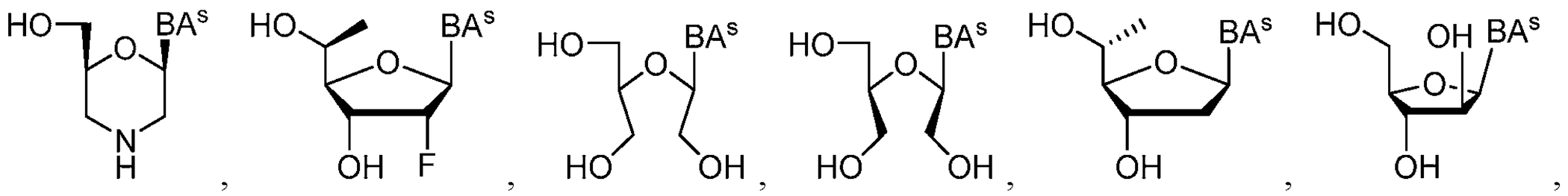
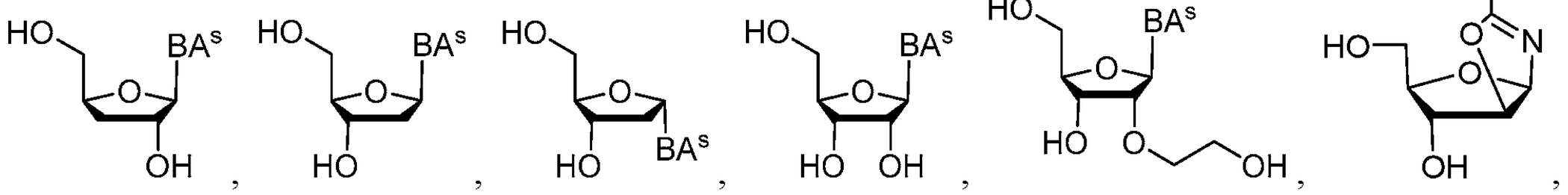
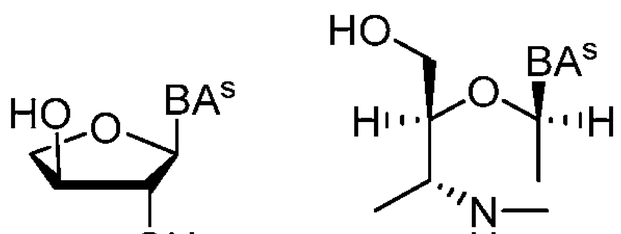
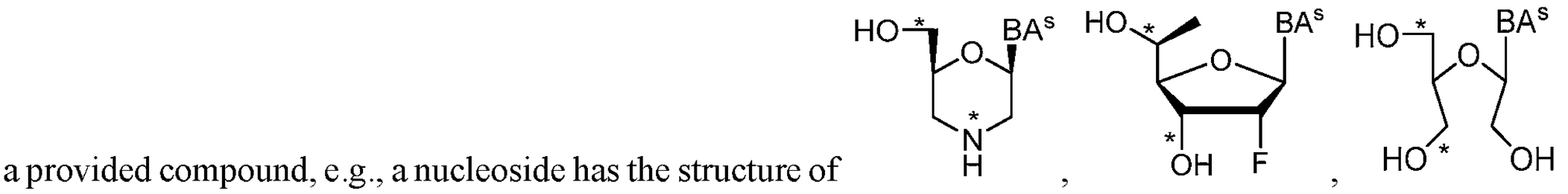
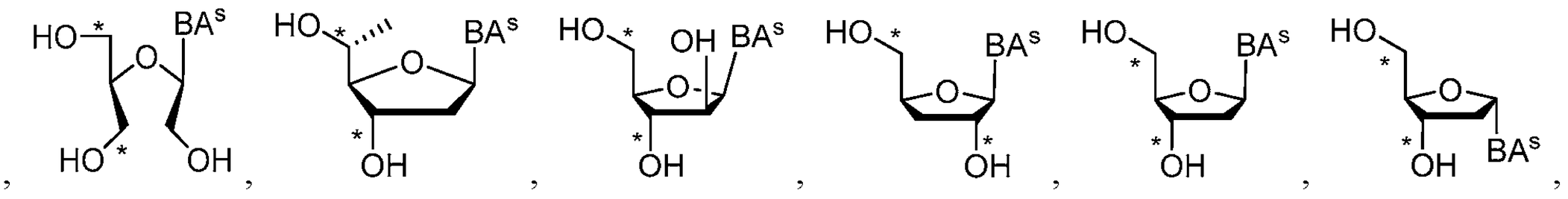
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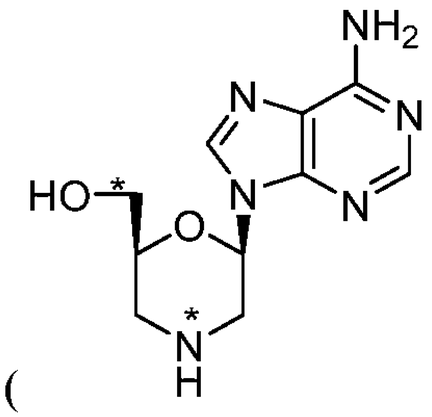
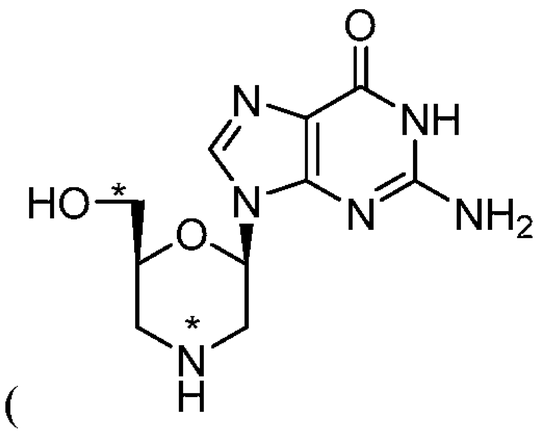
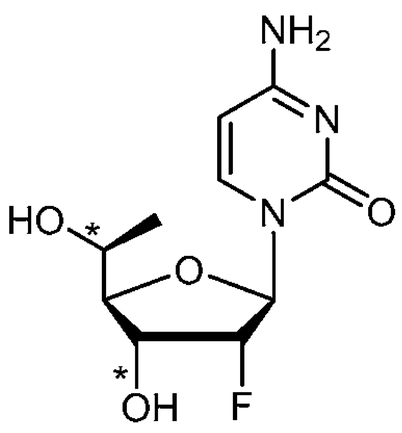
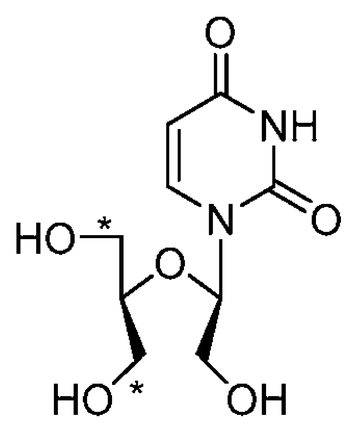
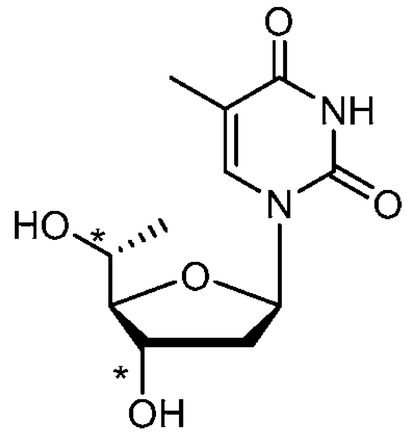
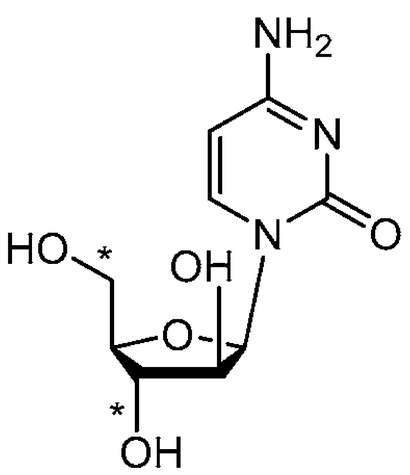
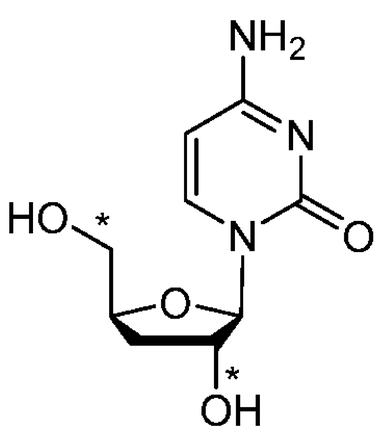
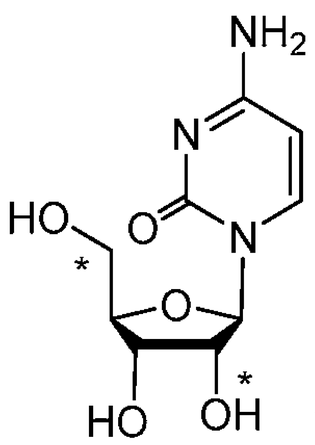
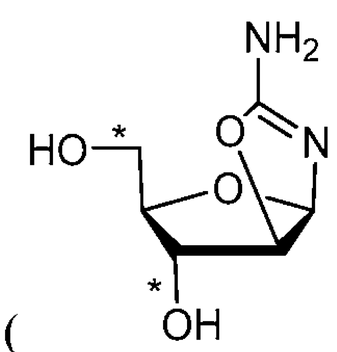
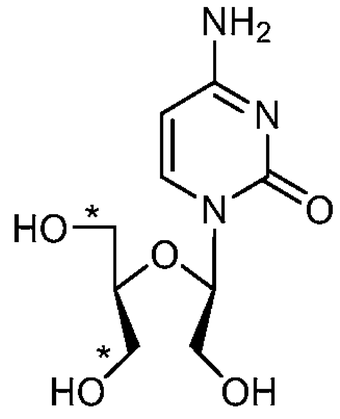
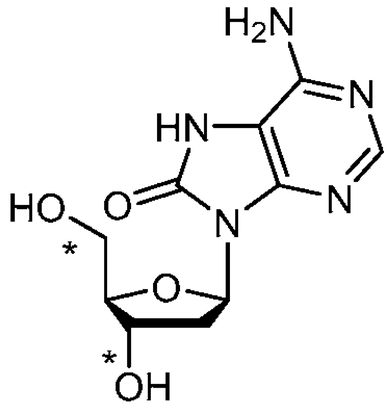
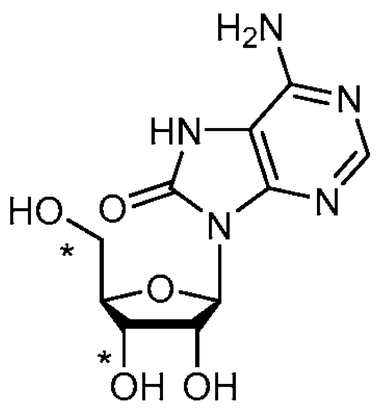
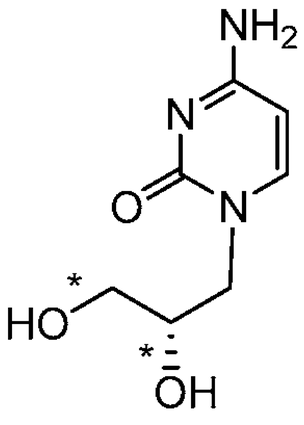
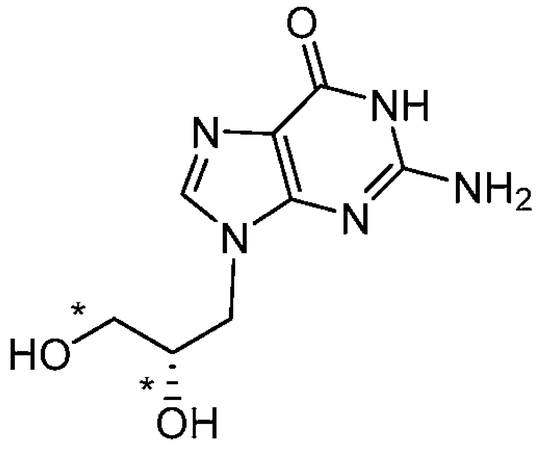
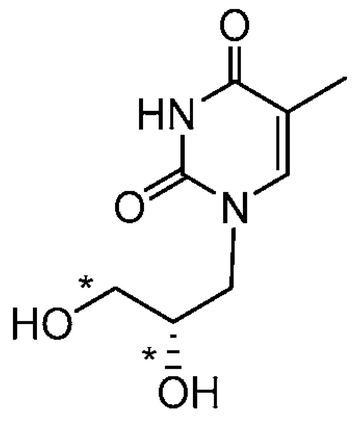
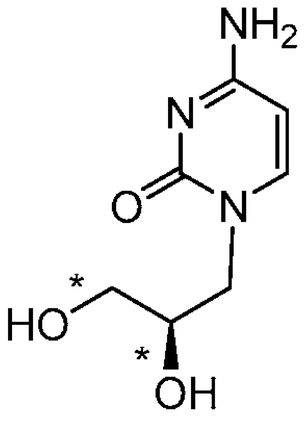
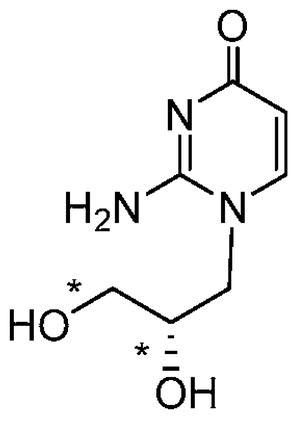
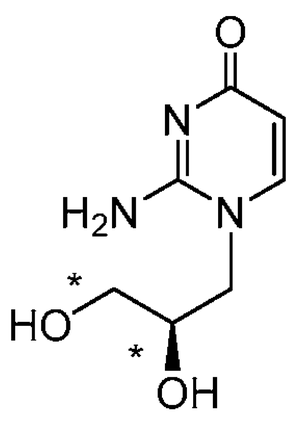
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b005U		b002I	
b006U		b003I	
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b001G		b007C	
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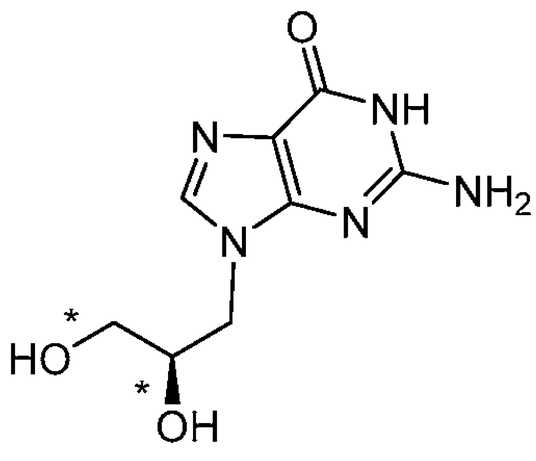
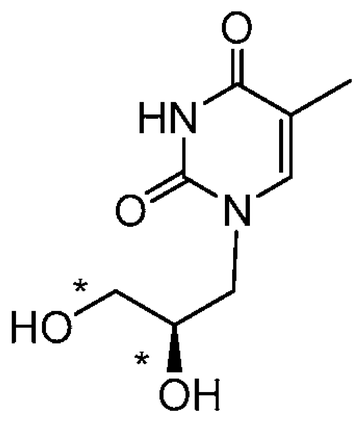
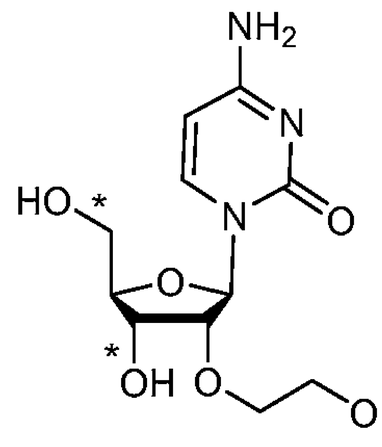
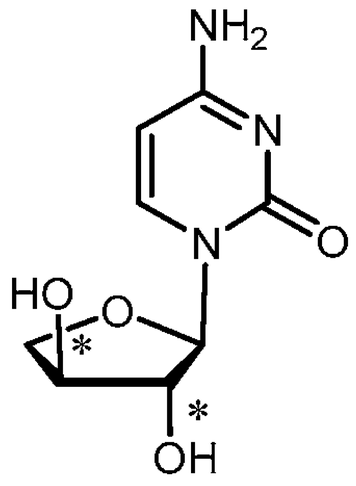
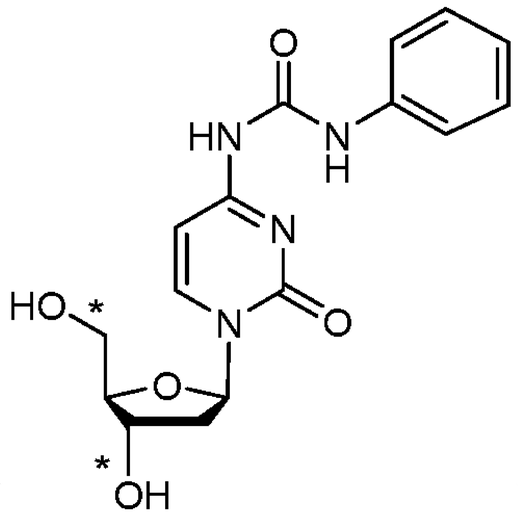
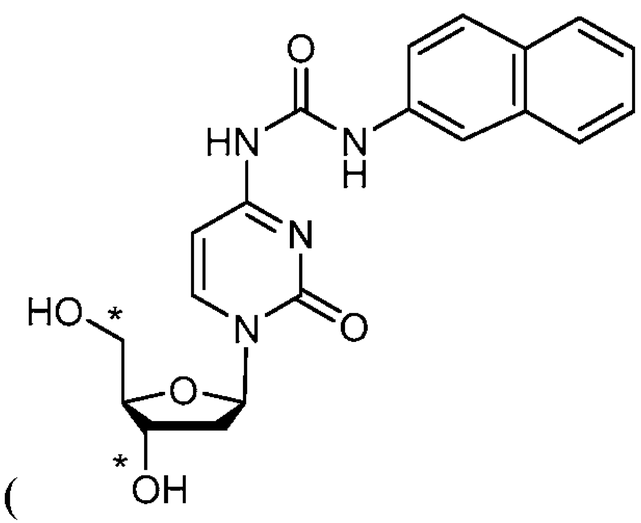
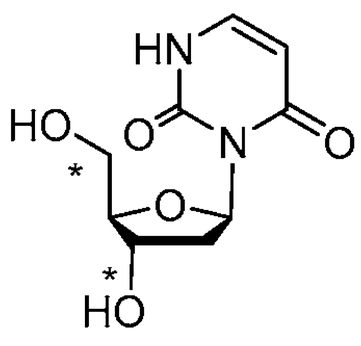
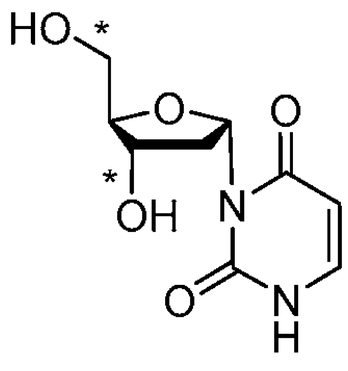
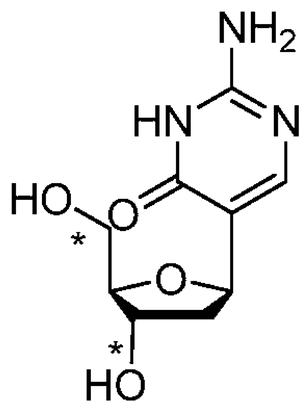
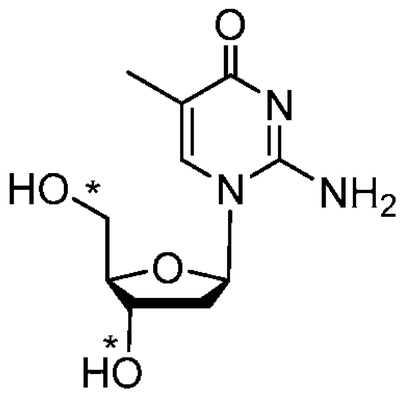
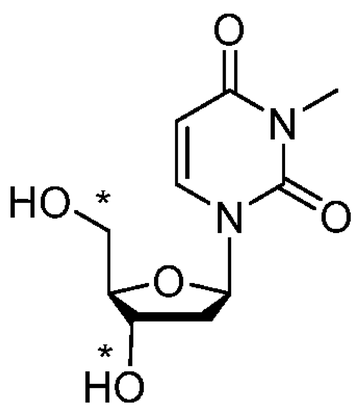
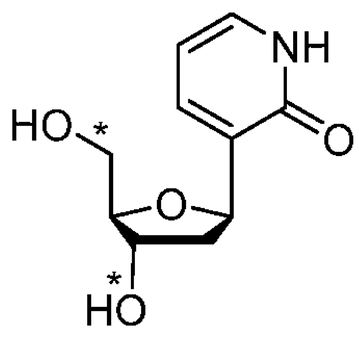
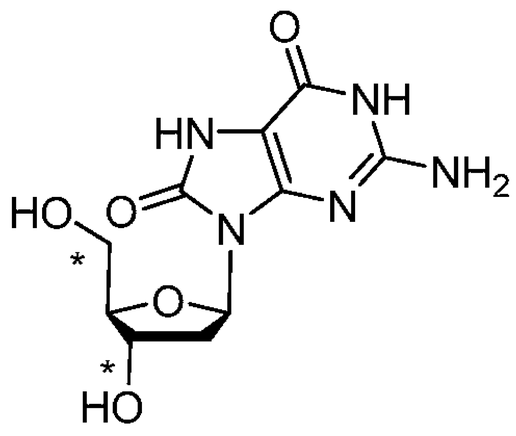
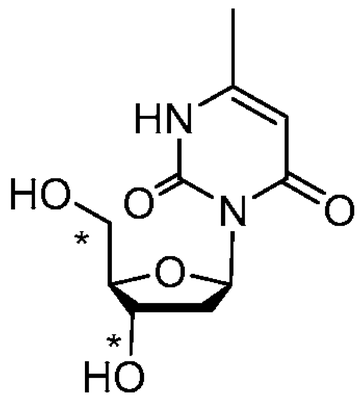
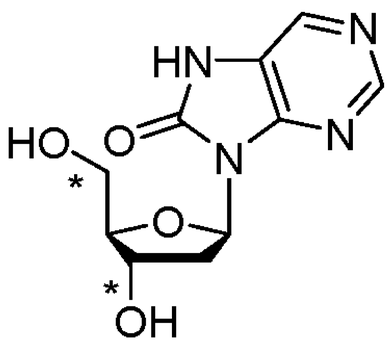
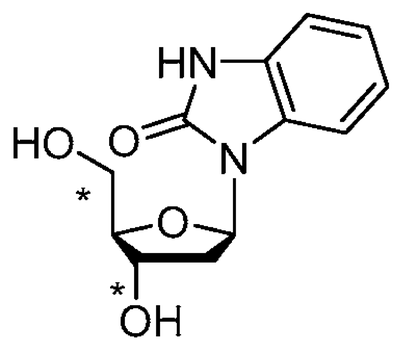
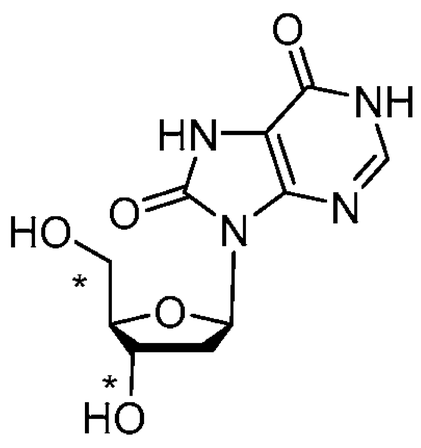
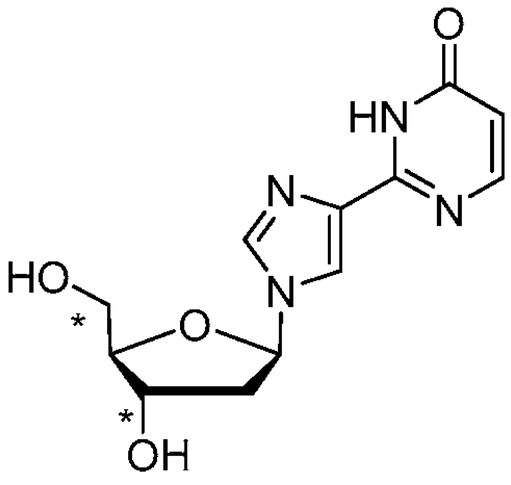
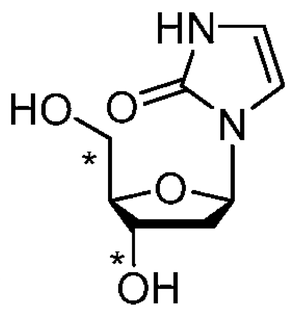
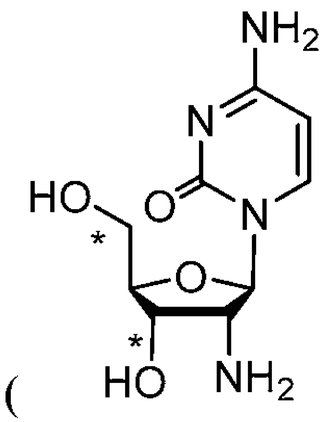
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b013U		b002G	
b004I		b009C	
b014I			

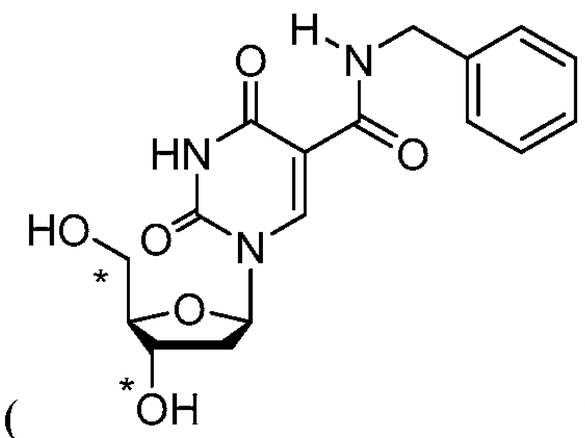
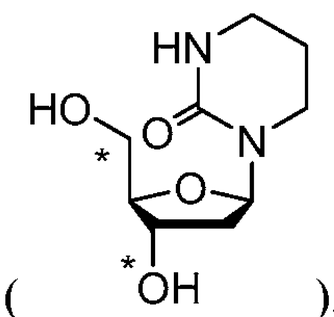
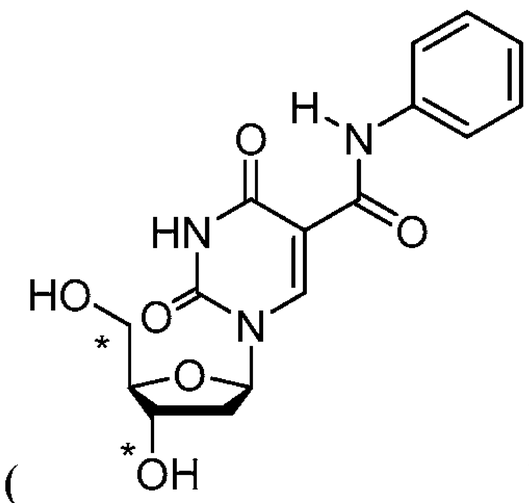
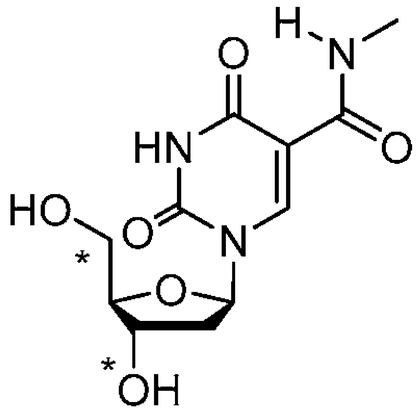
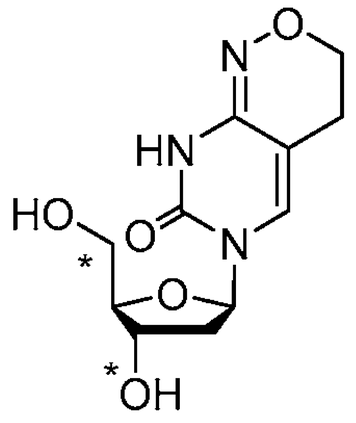
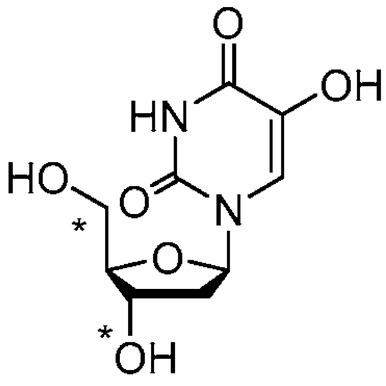
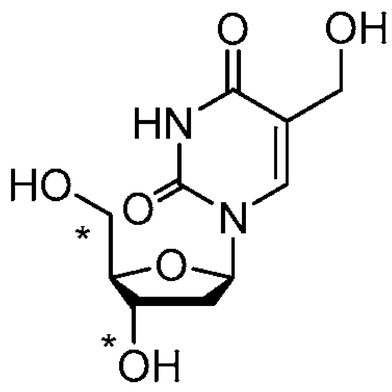
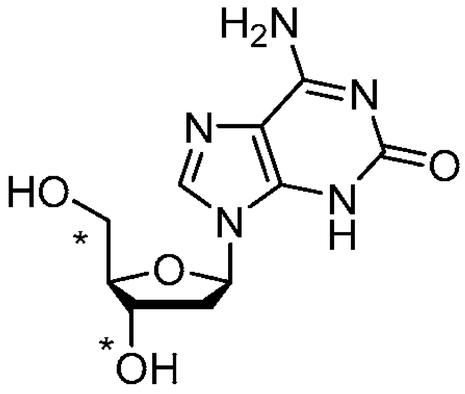
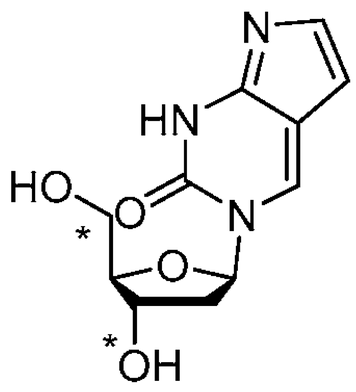
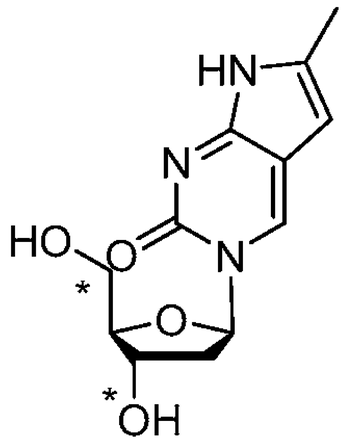
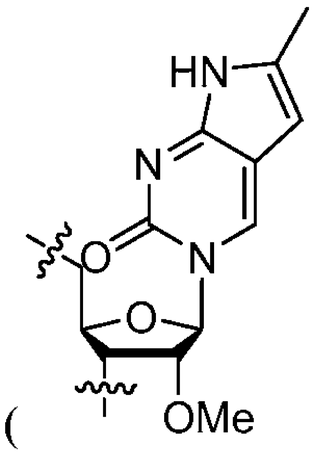
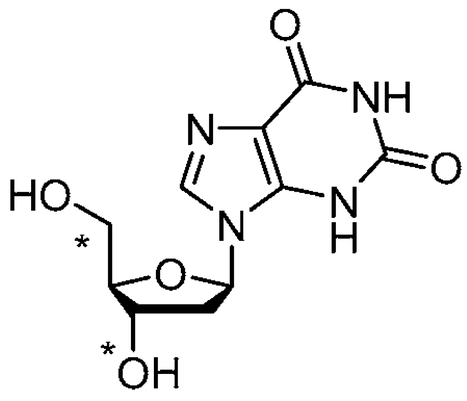
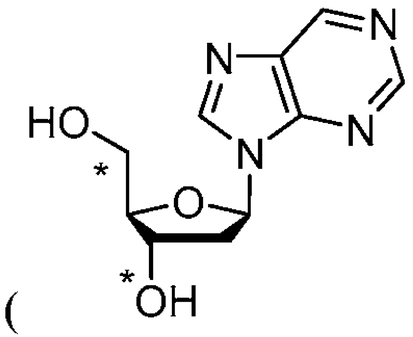
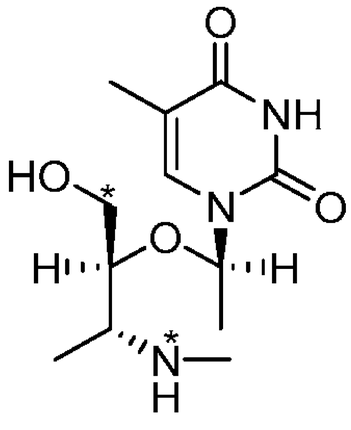
In some embodiments, a modified nucleobase is b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp. In some embodiments, a modified nucleobase is zdnp, b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, or b007C. In some embodiments, the present disclosure provides oligonucleotides comprising one or more such nucleobases. In some embodiments, the present disclosure provides compounds comprising such nucleobases. In some embodiments, the present disclosure provides monomers (e.g., those useful for oligonucleotide synthesis) comprising such nucleobases. In some embodiments, the present disclosure provides phosphoramidites comprising such nucleobases. In some embodiments, phosphoramidites are CED phosphoramidites. In some embodiments, monomers comprise auxiliary moieties as described herein (e.g., with P forming bonds to O and N, to O and S, to S and S, etc.). In some embodiments, phosphoramidites comprise chiral auxiliary moieties as described herein (e.g., with P forming bonds to O and N). In some embodiments, R^{NS} comprises such a nucleobase. In some embodiments, nucleobases are protected for oligonucleotide synthesis.

[00724] In some embodiments, the present disclosure provides various nucleosides. In some embodiments, b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, or b007C may also refer to a nucleoside whose nucleobase is

b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, or b007C, respectively. For example, b001A may refer to a nucleoside whose nucleobase is  and whose sugar is a natural DNA sugar; sugar modification may also be indicated, for example, "r" in b001rA indicates there is a 2'-OH on the sugar (a natural RNA sugar). In some embodiments, the present disclosure provides a compound having the structure of  ,  ,  , or , or a salt thereof, wherein BA^s is as described herein. In some embodiments, a provided compound, e.g., a nucleoside has the structure of  ,  , or a salt thereof, wherein "*" indicates connection to internucleotidic linkages when in various oligonucleotides, and BA^s is as described herein. In some embodiments, BA^s is a nucleobase, e.g., BA as described herein. In some embodiments, BA is protected for oligonucleotide synthesis. In some embodiments,

a provided nucleoside is selected from Asm01 (), Gsm01 (),
5MSfC (), Usm04 (), 5MRdT (), Csm15 (
), Csm16 (), rCsm14 (), L034 (),
Csm04 (), b001A (), b001rA (), Csm11 (
), Gsm11 (), Tsm11 (), Csm12 (
), b009Csm11 (), b009Csm12 (), Gsm12 (

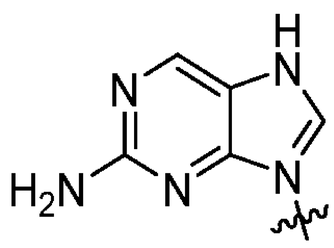
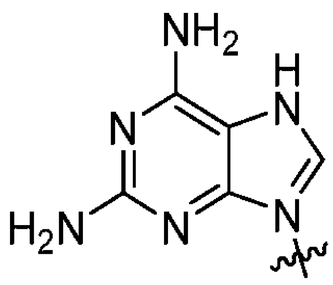

), Tsm12 (

), rCsm13 (

), Csm17 (

), b004C (

), b007C (

), b008U (

), b010U (

), b001C (

), b008C (

), b011U (

), b012U (

), b002G (

), b013U (

), b002A (

), b003A (

), b004I (

), b014I (

), b009U (

), aC (

),

b001U (), b002U (), b003U (), b004U (), b005U (), b006U (), b007U (), b001G (), b002C (), b003C (), b003mC (), b002I (), b003I () or Tsm18 (), or a salt thereof, wherein "*" indicates connection to internucleotidic linkages when in various oligonucleotides. In some embodiments, an oligonucleotide comprises a nucleoside described herein. In some embodiments, a nucleoside is connected to a internucleotidic linkage through a nitrogen atom (e.g., sm01, sm18, etc.), wherein the nitrogen atom is directly connected to a linkage phosphorus atom. In some embodiments, the present disclosure provides monomers of nucleosides (e.g., Asm01, Gsm01, Tsm18, etc.) as described herein. In some embodiments, the present disclosure provides phosphoramidites of nucleosides as described herein. In some embodiments, such monomers or phosphoramidites comprise protected hydroxyl (e.g., DMTrO−) and/or protected nucleobases (e.g., for oligonucleotide synthesis). In some

embodiments, such monomers or phosphoramidites comprise protected hydroxyl (e.g., DMTrO−), optionally protected nucleobases (e.g., as useful for oligonucleotide synthesis), and/or chiral auxiliary groups. Certain reagents, such as various phosphoramidites, that are useful for incorporating various nucleosides and/or compounds into oligonucleotides, and certain technolgoies for utilizing such reagents for oligonucleotide preparation, e.g., cycles, conditions, etc., are described in the Examples or WO 2021/071858. Certain oligonucleotides comprising modified nucleosides and compositions thereof are prepared utilizing such reagents and technologies and are presented herein as examples, e.g., those in various Tables including those in Table 1.

[00725] In some embodiments, the present disclosure provides oligonucleotides comprising one or more modified nucleobases as described herein. In some embodiments, the present disclosure provides compounds comprising modified nucleobases as described herein. In some embodiments, the present disclosure provides monomers (e.g., those useful for oligonucleotide synthesis) comprising modified nucleobases as described herein. In some embodiments, the present disclosure provides phosphoramidites comprising modified nucleobases as described herein. In some embodiments, phosphoramidites are CED phosphoramidites. In some embodiments, monomers comprise auxiliary moieties as described herein (e.g., with P forming bonds to O and N, to O and S, to S and S, etc.). In some embodiments, phosphoramidites comprise chiral auxiliary moieties as described herein (e.g., with P forming bonds to O and N). In some embodiments, R^{NS} comprises a nucleobase as described herein. In some embodiments, R^{NS} comprises a modified nucleobase as described herein. In some embodiments, nucleobases are protected for oligonucleotide synthesis.

[00726] In some embodiments, an oligonucleotide comprises one or more structures independently selected from pseudoisocytidine, Benner's base Z, 5-hydroxyC, 5-aminoC and 8-oxoA.

[00727] In some embodiments, a nucleobase is optionally substituted 2AP (2-amino purine, ) or DAP (2,6-diamino purine, ). In some embodiments, a nucleobase is optionally substituted 2AP. In some embodiments, a nucleobase is optionally substituted DAP. In some embodiments, a nucleobase is 2AP. In some embodiments, a nucleobase is DAP.

[00728] As appreciated by those skilled in the art, various nucleobases are known in the art and can be utilized in accordance with the present disclosure, e.g., those described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO

2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the sugar, base, and internucleotidic linkage modifications of each of which are independently incorporated herein by reference. In some embodiments, nucleobases are protected and useful for oligonucleotide synthesis.

[00729] In some embodiments, a nucleobase is a natural nucleobase or a modified nucleobase derived from a natural nucleobase. Examples include uracil, thymine, adenine, cytosine, and guanine optionally having their respective amino groups protected by acyl protecting groups, 2-fluorouracil, 2-fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurine, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products). Certain examples of modified nucleobases are disclosed in Chiu and Rana, RNA, 2003, 9, 1034-1048, Limbach et al. Nucleic Acids Research, 1994, 22, 2183-2196 and Revankar and Rao, Comprehensive Natural Products Chemistry, vol. 7, 313. In some embodiments, a modified nucleobase is substituted uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a modified nucleobase is a functional replacement, e.g., in terms of hydrogen bonding and/or base pairing, of uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a nucleobase is optionally substituted uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine. In some embodiments, a nucleobase is uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine.

[00730] In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytosine. In some embodiments, the present disclosure provides an oligonucleotide whose base sequence is disclosed herein, e.g., in Table 1, wherein each T may be independently replaced with U and vice versa, and each cytosine is optionally and independently replaced with 5-methylcytosine or vice versa. As appreciated by those skilled in the art, in some embodiments, 5mC may be treated as C with respect to base sequence of an oligonucleotide - such oligonucleotide comprises a nucleobase modification at the C position (e.g., see various oligonucleotides in Table 1). In description of oligonucleotides, typically unless otherwise noted, nucleobases, sugars and internucleotidic linkages are non-modified.

[00731] In some embodiments, a modified base is optionally substituted adenine, cytosine, guanine, thymine, or uracil, or a tautomer thereof. In some embodiments, a modified nucleobase is a modified adenine, cytosine, guanine, thymine or uracil, modified by one or more modifications by which:

a nucleobase is modified by one or more optionally substituted groups independently selected from acyl, halogen, amino, azide, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, heteroaryl, carboxyl, hydroxyl, biotin, avidin, streptavidin, substituted silyl, and combinations thereof;

one or more atoms of a nucleobase are independently replaced with a different atom selected from carbon, nitrogen and sulfur;

one or more double bonds in a nucleobase are independently hydrogenated; or

one or more aryl or heteroaryl rings are independently inserted into a nucleobase.

[00732] In some embodiments, a base is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms. In some embodiments, a modified base is optionally substituted A, T, C, G or U, wherein one or more $-NH_2$ are independently and optionally replaced with $-C(-L-R^1)_3$, one or more $-NH-$ are independently and optionally replaced with $-C(-L-R^1)_2-$, one or more $=N-$ are independently and optionally replaced with $-C(-L-R^1)-$, one or more $=CH-$ are independently and optionally replaced with $=N-$, and one or more $=O$ are independently and optionally replaced with $=S$, $=N(-L-R^1)$, or $=C(-L-R^1)_2$, wherein two or more $-L-R^1$ are optionally taken together with their intervening atoms to form a 3-30 membered bicyclic or polycyclic ring having 0-10 heteroatom ring atoms, wherein the modified base is different than the natural A, T, C, G and U. In some embodiments, a base is optionally substituted A, T, C, G or U. In some embodiments, a modified base is substituted A, T, C, G or U, wherein the modified base is different than the natural A, T, C, G and U.

[00733] In some embodiments, a modified nucleobase is a modified nucleobase known in the art, e.g., WO2017/210647. In some embodiments, modified nucleobases are expanded-size nucleobases in which one or more aryl and/or heteroaryl rings, such as phenyl rings, have been added. Certain examples of modified nucleobases, including nucleobase replacements, are described in the Glen Research catalog (Glen Research, Sterling, Virginia); Krueger AT et al., Acc. Chem. Res., 2007, 40, 141-150; Kool, ET, Acc. Chem. Res., 2002, 35, 936-943; Benner S.A., et al., Nat. Rev. Genet., 2005, 6, 553-543; Romesberg, F.E., et al., Curr. Opin. Chem. Biol., 2003, 7, 723-733; or Hirao, I., Curr. Opin. Chem. Biol., 2006, 10, 622-627. In some embodiments, an expanded-size nucleobase is an expanded-size nucleobase described in, e.g., WO2017/210647. In some embodiments, modified nucleobases are moieties such as corrin- or porphyrin-derived rings. Certain porphyrin-derived base replacements have been described in, e.g., Morales-Rojas, H and Kool, ET, Org. Lett., 2002, 4, 4377-4380. In some embodiments, a porphyrin-derived ring is a porphyrin-derived ring described in, e.g., WO2017/219647. In some embodiments, a modified nucleobase is a modified nucleobase described in, e.g., WO2017/219647. In some embodiments, a modified nucleobase is fluorescent. Examples of such fluorescent modified nucleobases include phenanthrene, pyrene, stillbene, isoxanthine, isozanthopterin, terphenyl, terthiophene, benzoterthiophene, coumarin, lumazine, tethered stillbene, benzo-uracil, naphtho-uracil, etc., and those described in e.g., WO2017/210647. In some embodiments, a nucleobase or modified nucleobase is selected from: C5-propyne T, C5-propyne C, C5-Thiazole, phenoxazine, 2-thio-thymine, 5-triazolylphenyl-thymine, diaminopurine, and N2-aminopropylguanine.

[00734] In some embodiments, a modified nucleobase is selected from 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6

substituted purines. In certain embodiments, modified nucleobases are selected from 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (−C≡C-CH_3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. In some embodiments, modified nucleobases are tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one or 9-(2-aminoethoxy)-l,3-diazaphenoxazine-2- one (G-clamp). In some embodiments, modified nucleobases are those in which the purine or pyrimidine base is replaced with other heterocycles, for example, 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine or 2- pyridone. In some embodiments, modified nucleobases are those disclosed in US 3687808, The Concise Encyclopedia Of Polymer Science And Engineering, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, Antisense Research and Applications, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; or in Chapters 6 and 15, Antisense Drug Technology, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

[00735] In some embodiments, modified nucleobases and methods thereof are those described in US 20030158403, US 3687808, US 4845205, US 5130302, US 5134066, US 5 175273, US 5367066, US 5432272, US 5434257, US 5457187, US 5459255, US 5484908, US 5502177, US 5525711, US 5552540, US 5587469, US 5594 121, US 5596091, US 5614617, US 5645985, US 5681941, US 5750692, US 5763588, US 5830653, or US 6005096.

[00736] In some embodiments, a modified nucleobase is substituted. In some embodiments, a modified nucleobase is substituted such that it contains, e.g., heteroatoms, alkyl groups, or linking moieties connected to fluorescent moieties, biotin or avidin moieties, or other protein or peptides. In some embodiments, a modified nucleobase is a "universal base" that is not a nucleobase in the most classical sense, but that functions similarly to a nucleobase. One example of a universal base is 3-nitropyrrole.

[00737] In some embodiments, nucleosides that can be utilized in provided technologies comprise modified nucleobases and/or modified sugars, e.g., 4-acetylcytidine; 5-(carboxyhydroxylmethyl)uridine; 2'-O-methylcytidine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; dihydrouridine; 2'-O-methylpseudouridine; beta,D-galactosylqueosine; 2'-O-methylguanosine; N^6-isopentenyladenosine; 1-methyladenosine; 1-methylpseudouridine; 1-methylguanosine; l-methylinosine; 2,2-dimethylguanosine; 2-methyladenosine; 2-methylguanosine; N^7-methylguanosine; 3-methyl-cytidine; 5-methylcytidine; 5-hydroxymethylcytidine; 5-formylcytosine; 5-carboxylcytosine; N^6-methyladenosine; 7-

methylguanosine; 5-methylaminoethyluridine; 5-methoxyaminomethyl-2-thiouridine; beta,D-mannosylqueosine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 2-methylthio-N^6-isopentenyladenosine; N-((9-beta,D-ribofuranosyl-2-methylthiopurine-6-yl)carbamoyl)threonine; N-((9-beta,D-ribofuranosylpurine-6-yl)-N-methylcarbamoyl)threonine; uridine-5-oxyacetic acid methylester; uridine-5-oxyacetic acid (v); pseudouridine; queosine; 2-thiocytidine; 5-methyl-2-thiouridine; 2-thiouridine; 4-thiouridine; 5-methyluridine; 2'-O-methyl-5-methyluridine; and 2'-O-methyluridine.

[00738] In some embodiments, a nucleobase, e.g., a modified nucleobase comprises one or more biomolecule binding moieties such as e.g., antibodies, antibody fragments, biotin, avidin, streptavidin, receptor ligands, or chelating moieties. In other embodiments, a nucleobase is 5-bromouracil, 5-iodouracil, or 2,6-diaminopurine. In some embodiments, a nucleobase comprises substitution with a fluorescent or biomolecule binding moiety. In some embodiments, a substituent is a fluorescent moiety. In some embodiments, a substituent is biotin or avidin.

[00739] Certain examples of nucleobases and related methods are described in US 3687808, 4845205, US 513030, US 5134066, US 5175273, US 5367066, US 5432272, US 5457187, US 5457191, US 5459255, US 5484908, US 5502177, US 5525711, US 5552540, US 5587469, US 5594121, US 5596091, US 5614617, US 5681941, US 5750692, US 6015886, US 6147200, US 6166197, US 6222025, US 6235887, US 6380368, US 6528640, US 6639062, US 6617438, US 7045610, US 7427672, US or US 7495088.

[00740] In some embodiments, an oligonucleotide comprises a nucleobase, sugar, nucleoside, and/or internucleotidic linkage which is described in any of: Gryaznov, S; Chen, J.-K. J. Am. Chem. Soc. 1994, 116, 3143; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Jepsen et al. 2004 Oligo. 14: 130-146; Jones et al. J. Org. Chem. 1993, 58, 2983; Koizumi et al. 2003 Nuc. Acids Res. 12: 3267-3273; Koshkin et al. 1998 Tetrahedron 54: 3607-3630; Kumar et al. 1998 Bioo. Med. Chem. Let. 8: 2219-2222; Lauritsen et al. 2002 Chem. Comm. 5: 530-531; Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Morita et al. 2001 Nucl. Acids Res. Supp. 1: 241-242; Morita et al. 2002 Bioo. Med. Chem. Lett. 12: 73-76; Morita et al. 2003 Bioo. Med. Chem. Lett. 2211-2226; Nielsen et al. 1997 Chem. Soc. Rev. 73; Nielsen et al. 1997 J. Chem. Soc. Perkins Transl. 1: 3423-3433; Obika et al. 1997 Tetrahedron Lett. 38 (50): 8735–8; Obika et al. 1998 Tetrahedron Lett. 39: 5401-5404; Pallan et al. 2012 Chem. Comm. 48: 8195-8197; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Seth, Punit P; Siwkowski, Andrew; Allerson, Charles R; Vasquez, Guillermo; Lee, Sam; Prakash, Thazha P; Kinberger, Garth; Migawa, Michael T; Gaus, Hans; Bhat, Balkrishen; et al. From Nucleic Acids Symposium Series (2008), 52(1), 553-554; Singh et al. 1998 Chem. Comm. 1247-1248; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Sorensen 2003 Chem. Comm. 2130-2131; Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338;

Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; WO 2007090071; or WO 2016/079181.

[00741] In some embodiments, an oligonucleotide comprises a modified nucleobase, nucleoside or nucleotide which is described in any of: Feldman et al. 2017 J. Am. Chem. Soc. 139: 11427-11433, Feldman et al. 2017 Proc. Natl. Acad. Sci. USA 114: E6478-E6479, Hwang et al. 2009 Nucl. Acids Res. 37: 4757-4763, Hwang et al. 2008 J. Am. Chem. Soc. 130: 14872-14882, Lavergne et al. 2012 Chem. Eur. J. 18: 1231-1239, Lavergne et al. 2013 J. Am. Chem. Soc. 135: 5408-5419, Ledbetter et al. 2018 J. Am. Chem. Soc. 140: 758-765, Malyshev et al. 2009 J. Am. Chem. Soc. 131: 14620-14621, Seo et al. 2009 Chem. Bio. Chem. 10: 2394-2400, e.g., d3FB, d2Py analogs, d2Py, d3MPy, d4MPy, d5MPy, d34DMPy, d35DMPy, d45DMPy, d5FM, d5PrM, d5SICS, dFEMO, dMMO2, dNaM, dNM01, dTPT3, nucleotides with 2'-azido, 2'-chloro, 2'-amino or arabinose sugars, isocarbostiryl-, napthyl- and azaindole-nucleotides, and modifications and derivatives and functionalized versions thereof, e.g., those in which the sugar comprises a 2'-modification and/or other modification, and dMMO2 derivatives with meta-chlorine, -bromine, -iodine, -methyl, or -propinyl substituents.

[00742] In some embodiments, a nucleobase comprises at least one optionally substituted ring which comprises a heteroatom ring atom. In some embodiments, a nucleobase comprises at least one optionally substituted ring which comprises a nitrogen ring atom. In some embodiments, such a ring is aromatic. In some embodiments, a nucleobase is bonded to a sugar through a heteroatom. In some embodiments, a nucleobase is bonded to a sugar through a nitrogen atom. In some embodiments, a nucleobase is bonded to a sugar through a ring nitrogen atom.

[00743] In some embodiments, an oligonucleotide comprises a nucleobase or modified nucleobase as described in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the bases and modified nucleobases of each of which are independently incorporated herein by reference.

[00744] In some embodiments, a nucleobase is an optionally substituted purine base residue. In some embodiments, a nucleobase is a protected purine base residue. In some embodiments, a nucleobase is an optionally substituted adenine residue. In some embodiments, a nucleobase is a protected adenine residue. In some embodiments, a nucleobase is an optionally substituted guanine residue. In some embodiments, a nucleobase is a protected guanine residue. In some embodiments, a nucleobase is an optionally substituted cytosine residue. In some embodiments, a nucleobase is a protected cytosine residue. In some embodiments, a nucleobase is an optionally substituted thymine residue. In some embodiments, a nucleobase is a protected thymine residue. In some embodiments, a nucleobase is an optionally substituted uracil residue. In some embodiments, a nucleobase is a protected uracil residue. In some embodiments, a nucleobase is an optionally substituted 5-methylcytosine residue. In some embodiments, a nucleobase is a protected 5-methylcytosine residue.

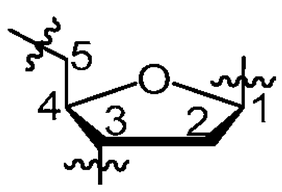
[00745] In some embodiments, a provided oligonucleotide comprises a modified nucleobase described in, e.g.,

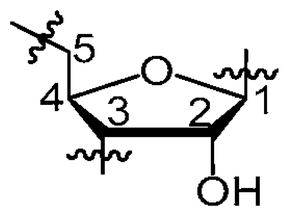
US 5552540, US 6222025, US 6528640, US 4845205, US 5681941, US 5750692, US 6015886, US 5614617, US 6147200, US 5457187, US 6639062, US 7427672, US 5459255, US 5484908, US 7045610, US 3687808, US 5502177, US 5525711 6235887, US 5175273, US 6617438, US 5594121, US 6380368, US 5367066, US 5587469, US 6166197, US 5432272, US 7495088, US 5134066, or US 5596091. In some embodiments, a nucleobase is described in WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376, and can be utilized in accordance with the present disclosure.

[00746] In some embodiments, a nucleobase is a protected base residue as used in oligonucleotide preparation. In some embodiments, a nucleobase is a base residue illustrated in US 2011/0294124, US 2015/0211006, US 2015/0197540, WO 2015/107425, WO 2017/192679, WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the base residues of each of which are independently incorporated herein by reference.

Sugars

[00747] Various sugars, including modified sugars, can be utilized in accordance with the present disclosure. In some embodiments, the present disclosure provides sugar modifications and patterns thereof optionally in combination with other structural elements (e.g., internucleotidic linkage modifications and patterns thereof, pattern of backbone chiral centers thereof, etc.) that when incorporated into oligonucleotides can provide improved properties and/or activities.

[00748] The most common naturally occurring nucleosides comprise ribose sugars (e.g., in RNA) or deoxyribose sugars (e.g., in DNA) linked to the nucleobases adenosine (A), cytosine (C), guanine (G), thymine (T) or uracil (U). In some embodiments, a sugar, e.g., various sugars in many oligonucleotides in Table 1 (unless otherwise notes), is a natural DNA sugar (in DNA nucleic acids or oligonucleotides, having the structure of 

, wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of an oligonucleotide, the 3' position may be connected to a 3'-end group (e.g., −OH). In some embodiments, a sugar is a natural RNA sugar (in RNA nucleic acids or oligonucleotides, having the structure of 

, wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of an oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of an oligonucleotide, the 3'

position may be connected to a 3'-end group (e.g., −OH). In some embodiments, a sugar is a modified sugar in that it is not a natural DNA sugar or a natural RNA sugar. Among other things, modified sugars may provide improved stability. In some embodiments, modified sugars can be utilized to alter and/or optimize one or more hybridization characteristics. In some embodiments, modified sugars can be utilized to alter and/or optimize target nucleic acid recognition. In some embodiments, modified sugars can be utilized to optimize Tm. In some embodiments, modified sugars can be utilized to improve oligonucleotide activities.

[00749] Among other things, the present disclosure demonstrates that various non-natural RNA sugars, such as natural DNA sugar, various modified sugars, etc., may be utilized in accordance with the present disclosure. For example, one or more natural DNA sugars can be tolerated at various positions. In some embodiments, incorporation of one or more natural DNA sugars provides increased levels of editing, or increased levels of editing by ADAR1 (p110, p150 or both), ADAR2, or both. In some embodiments, editing by ADAR1 is improved. In some embodiments, one or more sugars of N_{-3}, N_{-1}, N_1, N_4, N_5, N_7, N_8, N_{10}, N_{12}, N_{13}, N_{14}, N_{15}, N_{16}, N_{17}, N_{18}, N_{20}, and N_{21} is independently a natural DNA sugar (-(e.g., N_{-1}): counting from N_0 to the 3'-end of an oligonucleotide; + or just a number (e.g., N_1): counting from N_0 to the 5'-end of an oligonucleotide; each N_{NZ} is independently a nucleoside, wherein NZ is an integer from, e.g., about -100, -90, -80, -70, -60, -50, -40, -30, -20, -10, -9, -8, -7, -6, -5, -4, etc. to). In some embodiments, one or more sugars of N_{-3}, N_{-1}, N_0, N_1, N_4, N_5, N_7, N_8, N_{10}, N_{12}, N_{13}, N_{14}, N_{15}, N_{16}, N_{17}, N_{18}, N_{20}, and N_{21} is independently a natural DNA sugar. In some embodiments, one or more sugars of N_{-1}, N_5, N_{11}, N_{12} and N_{20} are independently a natural DNA sugar. In some embodiments, a sugar of N_{-1} is a natural DNA sugar. In some embodiments, a sugar of N_0 is a natural DNA sugar. In some embodiments, a sugar of N_1 is a natural DNA sugar. In some embodiments, a sugar of N_5 is a natural DNA sugar. In some embodiments, a sugar of N_{11} is a natural DNA sugar. In some embodiments, a sugar of N_{12} is a natural DNA sugar. In some embodiments, modified sugars are tolerated at one or more positions. In some embodiments, 2'-modified sugars, e.g., 2'-F and/or 2'-OR modified sugars are utilized at one or more or a majority of positions, wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl). In some embodiments, modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3'. In some embodiments, 2'-OR modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3' wherein R is optionally substituted C_{1-6} aliphatic (e.g., methyl). In some embodiments, modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3' and one or more 2'-F modified sugars, natural DNA sugars and/or natural RNA sugars are utilized in 5'-$N_1N_0N_{-1}$-3'. In some embodiments, modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3' and each sugar of 5'-$N_1N_0N_{-1}$-3' is independently a 2'-F modified sugar, a natural DNA sugar or a natural RNA sugar. In some embodiments, modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3' and each sugar of 5'-$N_1N_0N_{-1}$-3' is independently a 2'-F modified sugar or a natural DNA sugar. In some embodiments, modified sugars are utilized at one or more or a majority of or all positions out of 5'-$N_1N_0N_{-1}$-3' and each sugar of 5'-$N_1N_0N_{-1}$-3' is independently a natural DNA sugar. In some embodiments, modified sugars, e.g., 2'-OR modified sugars (wherein R is optionally

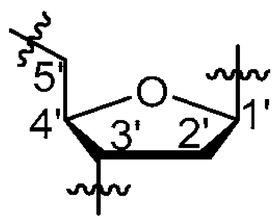
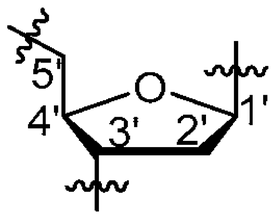
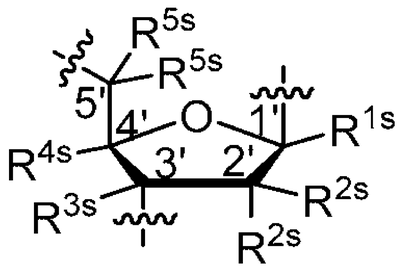
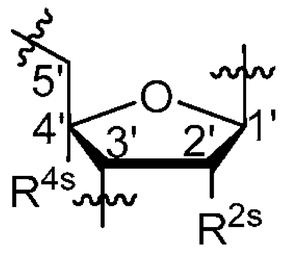
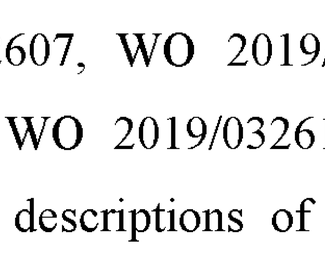
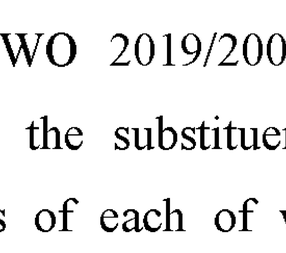
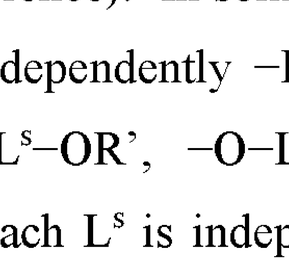
substituted C_{1-6} alkyl) provide increased levels of editing, or increased levels of editing by ADAR1 (p110, p150 or both), ADAR2, or both. In some embodiments, editing by ADAR2 is improved. In some embodiments, a modified sugar is a bicyclic sugar (e.g., a LNA sugar, a cEt sugar, etc.). In some embodiments, a bicyclic sugar may be utilized at one or more or all positions where a 2'-OR sugar is utilized, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, 2'-OR is 2'-OMe. In some embodiments, 2'-OR is 2'-MOE. In some embodiments, a majority is at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% (e.g., 55%-100%, 60%-100%, 70-100%, 75%-100%, 80%-100%, 90%-100%, 95%-100%, 60%-95%, 70%-95%, 75-95%, 80-95%, 85-95%, 90-95%, 51%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, etc.

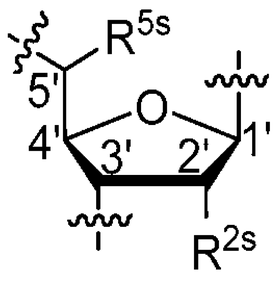
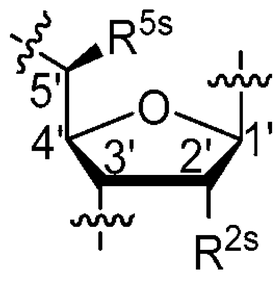
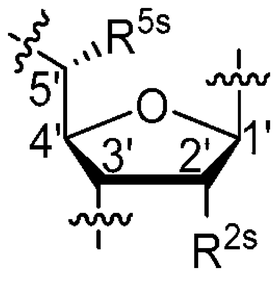
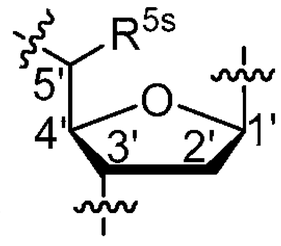
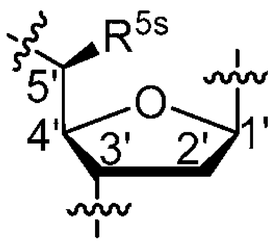
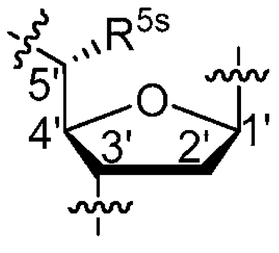
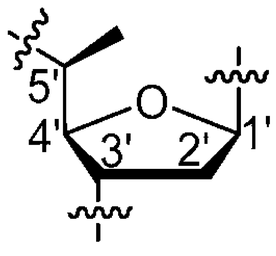
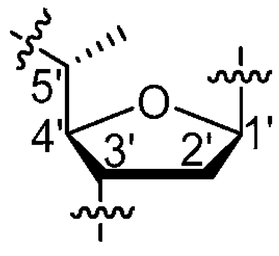
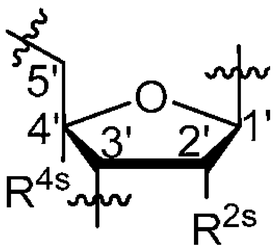
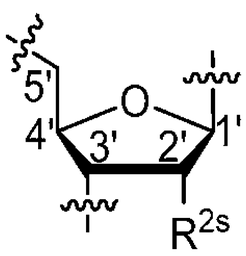
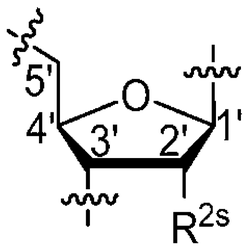
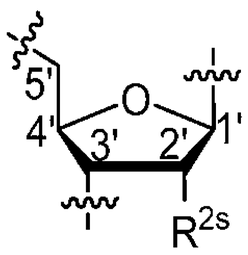
[00750] In some embodiments, one or more (e.g., 1-10, 1, 2, 3, 4, or 5, etc.) of the first several (e.g., 1-10, 1, 2, 3, 4, or 5, etc.) sugars (unless otherwise specified, from the 5'-end) of a provided oligonucleotide or of a first domain are independently modified sugars. In some embodiments, each of the first several sugars is independently a modified sugar. In some embodiments, the first one, two or three sugars of a provided oligonucleotide or of a first domain are independently modified sugars. In some embodiments, the first sugar is a modified sugar. In some embodiments, the first two sugars are independently modified sugars. In some embodiments, the first three sugars are independently modified sugars (e.g., WV-27458). In some embodiments, a modified sugar is a bicyclic sugar. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, each modified sugar is independently a 2'-modified sugar. In some embodiments, a modified sugar is a 2'-OMe modified sugar. In some embodiments, each modified sugar is a 2'-OMe modified sugar. In some embodiments, a modified sugar is a 2'-MOE modified sugar. In some embodiments, each modified sugar is a 2'-MOE modified sugar. In some embodiments, each modified sugar is independently a 2'-OMe or 2'-MOE modified sugar.

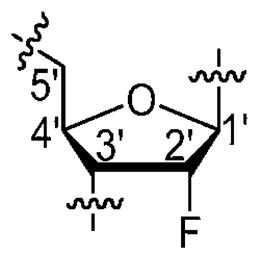
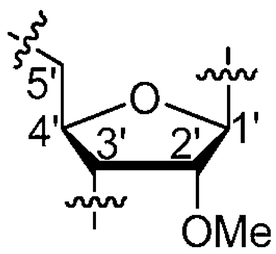
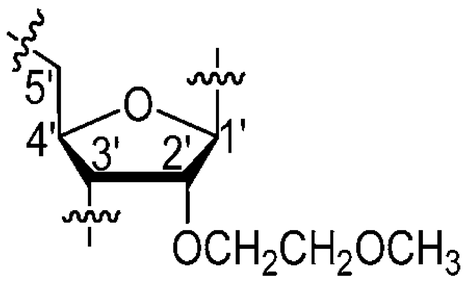
[00751] In some embodiments, one or more (e.g., 1-10, 1, 2, 3, 4, or 5, etc.) of the last several (e.g., 1-10, 1, 2, 3, 4, or 5, etc.) sugars (unless otherwise specified, from the 5'-end) of a provided oligonucleotide or of a second domain or a third subdomain are independently modified sugars. In some embodiments, each of the last several sugars is independently a modified sugar. In some embodiments, the last one, two or three sugars of a provided oligonucleotide or of a second domain or a third subdomain are independently modified sugars. In some embodiments, the last sugar is a modified sugar. In some embodiments, the last two sugars are independently modified sugars. In some embodiments, the last three sugars are independently modified sugars. In some embodiments, the last four sugars are independently modified sugars (e.g., WV-27458). In some embodiments, a modified sugar is a bicyclic sugar. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, each modified sugar is independently a 2'-modified sugar. In some embodiments, a modified sugar is a 2'-OMe modified sugar. In some embodiments, each modified sugar is a 2'-OMe modified sugar. In some embodiments, a modified sugar is a 2'-MOE modified sugar. In some embodiments, each modified sugar is a 2'-MOE modified sugar. In some embodiments, each modified sugar is independently a 2'-OMe or 2'-MOE modified sugar.

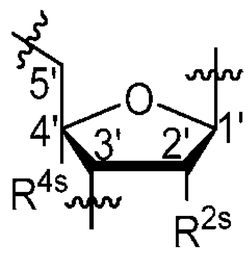
[00752] Sugars can be bonded to internucleotidic linkages at various positions. As non-limiting examples,

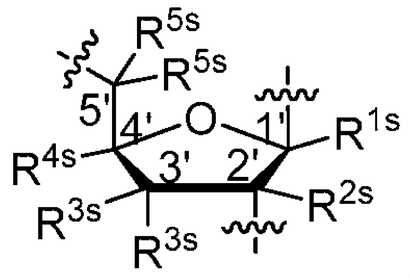
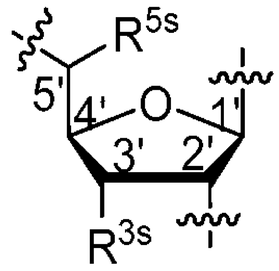
internucleotidic linkages can be bonded to the 2', 3', 4' or 5' positions of sugars. In some embodiments, as most commonly in natural nucleic acids, an internucleotidic linkage connects with one sugar at the 5' position and another sugar at the 3' position unless otherwise indicated.

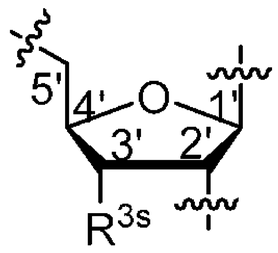
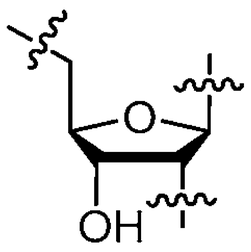
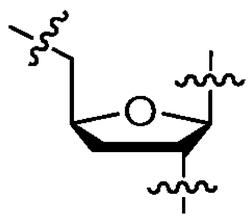
[00753] In some embodiments, a sugar is an optionally substituted natural DNA or RNA sugar. In some embodiments, a sugar is optionally substituted  . In some embodiments, the 2' position is optionally substituted. In some embodiments, a sugar is  . In some embodiments, a sugar has the structure of  or  , wherein each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently −H, a suitable substituent or suitable sugar modification (e.g., those described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the substituents, sugar modifications, descriptions of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s}, and modified sugars of each of which are independently incorporated herein by reference). In some embodiments, each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently R^s, wherein each R^s is independently −F, −Cl, −Br, −I, −CN, $-N_3$, −NO, $-NO_2$, $-L^s-R'$, $-L^s-OR'$, $-L^s-SR'$, $-L^s-N(R')_2$, $-O-L^s-OR'$, $-O-L^s-SR'$, or $-O-L^s-N(R')_2$, wherein each R' is independently as described herein, and each L^s is independently a covalent bond or optionally substituted bivalent C_{1-6} aliphatic or heteroaliphatic having 1-4 heteroatoms; or two R^s are taken together to form a bridge $-L^s-$. In some embodiments, R' is optionally substituted C_{1-10} aliphatic. In some embodiments, a sugar has the structure of  . In some embodiments, a sugar has the structure of  . In some embodiments, a sugar has the structure of  . In some embodiments, a sugar has the structure of


. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. In some embodiments, R^{5s} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5s} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{5s} is optionally substituted methyl. In some embodiments, R^{5s} is methyl. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. In some embodiments, a sugar has the structure of 
. Various such sugars are utilized in Table 1. In some embodiments, a sugar has the structure of 
. In some embodiments, a 2'-modified sugar has the structure of 
, wherein R^{2s} is a 2'-modification. In some embodiments, a sugar has the structure of 
, wherein R^{2s} is −H, halogen, or −OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −OMe. In some

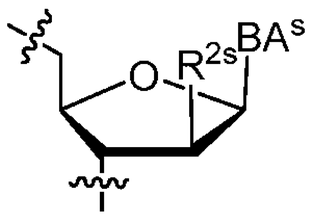
embodiments, a modified nucleoside is mA, mT, mC, m5mC, mG, mU, etc., in which R^{2s} is −OMe. In some embodiments, R^{2s} is $-OCH_2CH_2OMe$. In some embodiments, a modified nucleoside is Aeo, Teo, Ceo, m5Ceo, Geo, Ueo, etc., in which R^{2s} is $-OCH_2CH_2OMe$. In some embodiments, R^{2s} is $-OCH_2CH_2OH$. In some embodiments, an oligonucleotide comprises a 2'-F modified sugar having the structure of  (e.g., as in fA, fT, fC, f5mC, fG, fU, etc.). In some embodiments, an oligonucleotide comprises a 2'-OMe modified sugar having the structure of  (e.g., as in mA, mT, mC, m5mC, mG, mU, etc.). In some embodiments, an oligonucleotide comprises a 2'-MOE modified sugar having the structure of  (e.g., as in Aeo, Teo, Ceo, m5Ceo, Geo, Ueo, etc.).

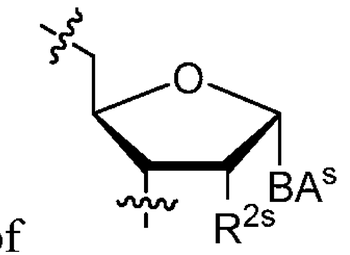
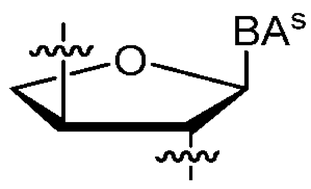
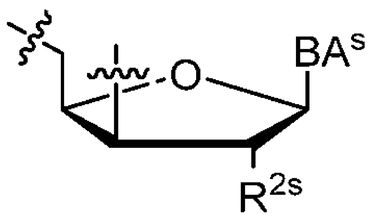
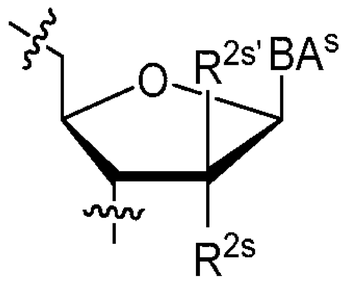
[00754] In some embodiments, a sugar has the structure of  , wherein R^{2s} and R^{4s} are taken together to form $-L^s-$, wherein L^s is a covalent bond or optionally substituted bivalent C_{1-6} aliphatic or heteroaliphatic having 1-4 heteroatoms. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen or sulfur). In some embodiments, L^s is optionally substituted C2−O−CH_2−C4. In some embodiments, L^s is C2−O−CH_2−C4. In some embodiments, L^s is C2−O−(*R*)-$CH(CH_2CH_3)$−C4. In some embodiments, L^s is C2−O−(*S*)-$CH(CH_2CH_3)$−C4.

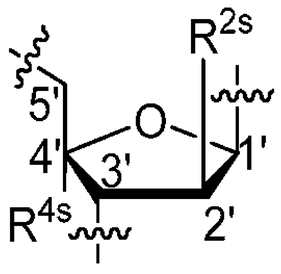
[00755] In some embodiments, a sugar has the structure of  , wherein each variable is independently as described herein. In some embodiments, a sugar has the structure of  , wherein each variable is independently as described herein. In some embodiments, R^{5s} is −H. In some embodiments,

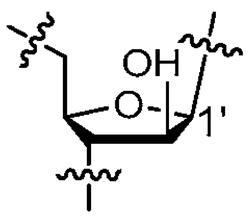
a sugar has the structure of  , wherein each variable is independently as described herein. In some embodiments, R^{3s} is −OH. In some embodiments, R^{3s} is −H. In some embodiments, a sugar is  . In some embodiments, a sugar is  .

[00756] In some embodiments, a sugar is

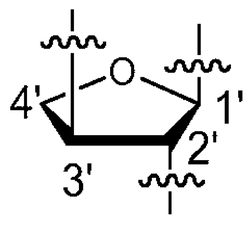


[00757] In some embodiments, a nucleoside comprising a modified sugar has the structure of or a salt form thereof, wherein BA^s is −H or an optionally substituted or protected nucleobase (e.g., BA), and R^{2s} is as described herein. In some embodiments, R^{2s} is −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, BA^s is −H. In some embodiments, BA^s is an optionally substituted or protected nucleobase. In some embodiments, BA^s is BA. In some embodiments, R^{2s} is −F. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein each variable is independently as described herein. In some embodiments, R^{2s} is −H, −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −F. In some embodiments, a nucleoside comprising a modified sugar has the structure of  , wherein each variable is as described herein. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein each variable is independently as described herein. In some embodiments, R^{2s} is −H, −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −F. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein $R^{2s'}$ is R^s, and each of R^s, R^{2s} and BA^s is independently as described herein. In some embodiments, each of R^{2s} and $R^{2s'}$ is independently

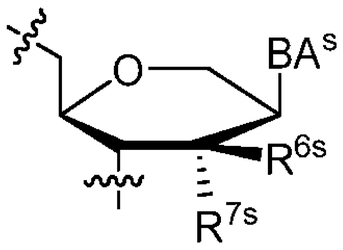
−H, −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −OH. In some embodiments, R^{2s} is halogen. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is optionally substituted C_1-C_6 alkoxy. In some embodiments, $R^{2s'}$ is −H. In some embodiments, $R^{2s'}$ is −OH. In some embodiments, $R^{2s'}$ is halogen. In some embodiments, $R^{2s'}$ is −F. In some embodiments, $R^{2s'}$ is optionally substituted C_1-C_6 alkoxy. In some embodiments, BA^s is −H. In some embodiments, BA^s is an optionally substituted or protected nucleobase. In some embodiments, BA^s is BA. In some embodiments, nucleobases such as BA are optionally substituted or protected for oligonucleotide synthesis. Certain such nucleosides including sugars and nucleobases and uses thereof are described in WO 2020/154342. In some embodiments, an oligonucleotide comprises arabinoside, 2'-deoxy-2'-fluoro-arabinoside, 2'-OR arabinoside, adeoxycytidine, DNA-abasic, RNA-abasic, or 2'-OR abasic, wherein R is not hydrogen (e.g., optionally substituted C_{1-6} aliphatic). In some embodiments, 2'-OR is 2'-OMe. In some embodiments, 2'-OR is 2'-MOE. In some embodiments, an oligonucleotide comprises 2'-O-methyl-arabinocytidine (amC). In some embodiments, oligonucleotides comprise such nucleosides. In some embodiments, monomers comprise such nucleosides. In some embodiments, phosphoramidites comprise such nucleosides (in some embodiments, one connecting site (e.g., a $-CH_2-$ connecting site) is bonded to an optionally substituted −OH, e.g., (−ODMTr), and one connecting site (e.g., a ring connecting site) is bonded to O which is also bonded to P of a phosphoramidite). In some embodiments, one or more or each of a 5' immediate nucleoside (e.g., N_1), an opposite nucleoside (N_0) and a 3' immediate nucleoside (e.g., N_{-1}) is independently such a nucleoside. In some embodiments, 5'-$N_1N_0N_{-1}$-3' is amCCA. In some embodiments, a sugar has the structure of 

, wherein each variable is as described herein and C1' is bonded to a nucleobase. In some embodiments, a sugar is an arabinose. In some embodiments, a sugar has the structure of 

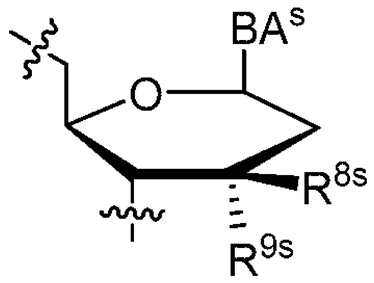
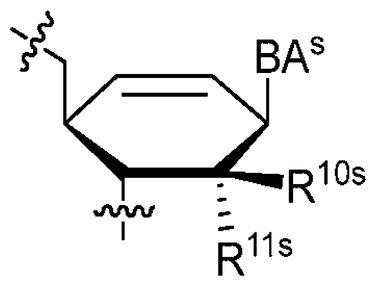
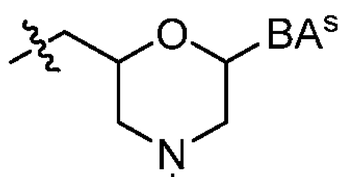
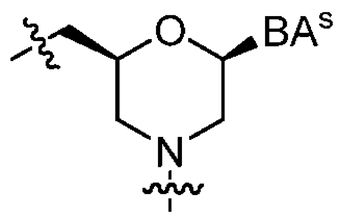
, wherein C1' is bonded to a nucleobase.

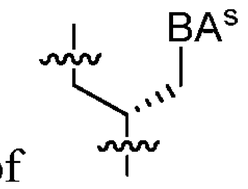
[00758] In some embodiments, a sugar is 

, wherein a nucleobase is bonded at position 1'.

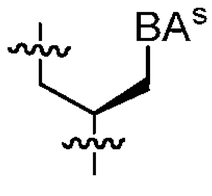
[00759] In some embodiments, a nucleoside comprising a modified sugar has the structure of 

or a salt form thereof, wherein each of R^{6s} and R^{7s} is independently R^s, BA^s is −H or an optionally substituted or protected nucleobase (e.g., BA), and R^s is independently as described herein. In some

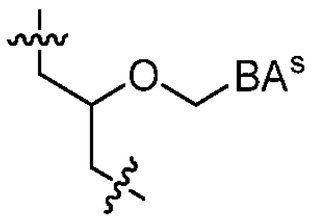
embodiments, R^{6s} is −H, −OH or halogen, and R^{7s} is −H, −OH, halogen or optionally substituted C_1-C_6 alkoxy. In some embodiments, BA^s is −H. In some embodiments, BA^s is an optionally substituted or protected nucleobase. In some embodiments, BA^s is BA. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein each of R^{8s} and R^{9s} is independently R^s, and each of R^s and BA^s is independently as described herein. In some embodiments, R^{8s} is −H or halogen, and R^{9s} is −H, −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein each of R^{10s} and R^{11s} is independently R^s, and each of R^s and BA^s is independently as described herein. In some embodiments, R^{10s} is −H or halogen, and R^{11s} is −H, −OH, halogen, or optionally substituted C_1-C_6 alkoxy. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein BA^s is as described herein. In some embodiments, a nucleoside comprising a modified sugar has the structure of  or a salt form thereof, wherein BA^s is as described herein. Those skilled in the art appreciate that in some embodiments, the nitrogen may be directly bonded to linkage phosphorus. In some embodiments, a halogen is −F. In some embodiments, BA^s is −H. In some embodiments, BA^s is an optionally substituted or protected nucleobase. In some embodiments, BA^s is BA. In some embodiments, nucleobases such as BA are optionally substituted or protected for oligonucleotide synthesis. In some embodiments, an oligonucleotide comprises alpha-homo-DNA, beta-homo-DNA moieties. Certain such nucleosides including sugars and nucleobases and uses thereof are described in WO 2020/154343. In some embodiments, oligonucleotides comprise such nucleosides. In some embodiments, monomers comprise such nucleosides. In some embodiments, phosphoramidites comprise such nucleosides (in some embodiments, one connecting site (e.g., a $-CH_2-$ connecting site) is bonded to an optionally substituted −OH, e.g., −ODMTr, and one connecting site (e.g., a ring connecting site) is bonded to P of a phosphoramidite (e.g., when the connecting ring atom is N) or to O which is also bonded to P of a phosphoramidite(e.g., when the connecting ring atom is C)). In some embodiments, one or more or each of a 5' immediate nucleoside (e.g., N_1), an opposite nucleoside (N_0) and a 3' immediate nucleoside (e.g., N_{-1}) is independently such a nucleoside.



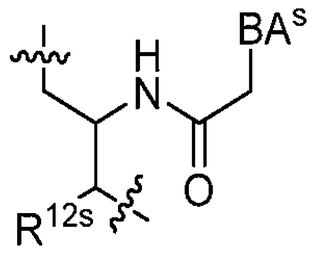
[00760] In some embodiments, a nucleoside comprising a modified sugar has the structure of or a salt form thereof, wherein each variable is as described herein. In some embodiments, a nucleoside



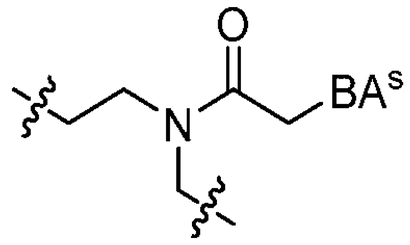
comprising a modified sugar has the structure of or a salt form thereof, wherein each variable is as described herein. In some embodiments, a nucleoside comprising a modified sugar has the structure of



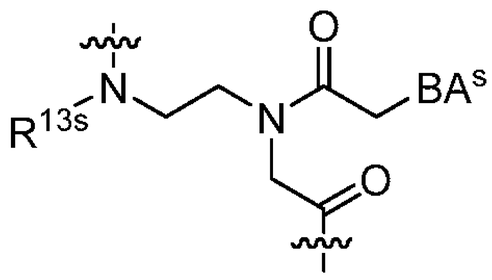
or a salt form thereof, wherein each variable is as described herein. In some embodiments, a



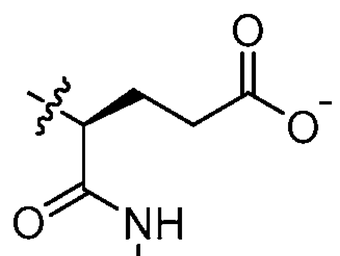
nucleoside comprising a modified sugar has the structure of or a salt form thereof, wherein R^{12s} is R^s, and each of R^s and BA^s is independently as described herein. In some embodiments, R^{12s} is −H, −OH, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, or optionally substituted C_{1-6} alkoxy. In some embodiments, a halogen is −F. In some embodiments, a nucleoside



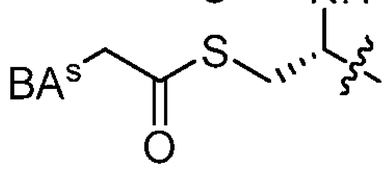
comprising a modified sugar has the structure of or a salt form thereof, wherein each variable is as described herein. In some embodiments, a nucleotide comprising a modified sugar has the



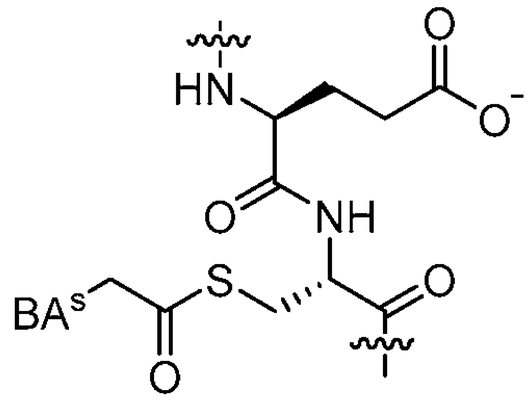
structure of or a salt form thereof, wherein R^{13s} is R^s, and each of R^s and BA^s is independently as described herein. In some embodiments, R^{13s} is −H or optionally substituted C_1-C_6 alkyl. In

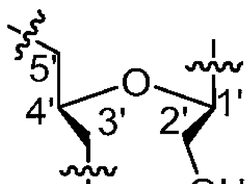
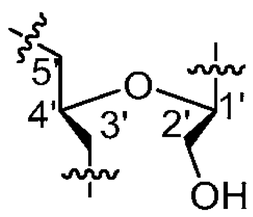
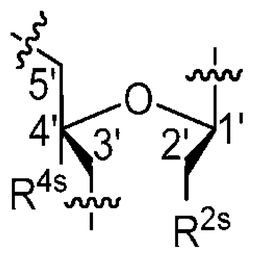
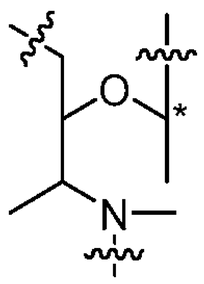
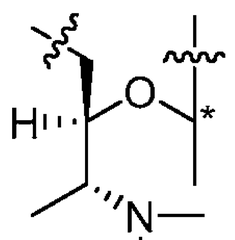


some embodiments, a nucleoside comprising a modified sugar has the structure of



or a salt form thereof, wherein each variable is as described herein. In some embodiments, a nucleotide

comprising a modified sugar has the structure of  or a salt form thereof, wherein each variable is as described herein. In some embodiments, a linkage is an amide linkage. In some embodiments, BA^s is −H. In some embodiments, BA^s is an optionally substituted or protected nucleobase. In some embodiments, BA^s is BA. In some embodiments, nucleobases such as BA are optionally substituted or protected for oligonucleotide synthesis. Certain such nucleosides and nucleotides including sugars and nucleobases and uses thereof are described in WO 2020/154344. In some embodiments, oligonucleotides comprise such nucleosides. In some embodiments, oligonucleotides comprise such nucleosides (in some embodiments, one connecting site (e.g., a $-CH_2-$ connecting site) is bonded to an optionally substituted −OH, e.g., (−ODMTr), and one connecting site (e.g., a ring connecting site) is bonded to O which is also bonded to P of a phosphoramidite. In some embodiments, one or more or each of a 5' immediate nucleoside (e.g., N_1), an opposite nucleoside (N_0) and a 3' immediate nucleoside (e.g., N_{-1}) is independently such a nucleoside.

[00761] In some embodiments, a sugar is an acyclic sugar, e.g. a UNA sugar. In some embodiments, a sugar is optionally substituted  . In some embodiments, the 2' position is optionally substituted. In some embodiments, a sugar is  . In some embodiments, a sugar has the structure of  . In some embodiments, R^{2s} is −OH. In some embodiments, a sugar is  , wherein "*" indicates the carbon atom bonded to a nucleobase. In some embodiments, a sugar is  , wherein "*" indicates the carbon atom bonded to a nucleobase. In some embodiments, the carbon atom bonded to a nitrogen atom of a nucleobase and is of *R* consiguration (e.g., sm18). In some embodiments, an oligonucleotide comprises a sugar described herein.

[00762] In some embodiments, a sugar is connected not through 5' and 3' positions. Those skilled in the art appreciate that for such sugars, 5' can refer to the side/direction toward 5'-end of an oligonucleotide, and 3'

can refer to the side/direction toward to 3'-end of an oligonucleotide.

[00763] In some embodiments, each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently R^s, wherein R^s is independently −H, halogen, −CN, $-N_3$, −NO, $-NO_2$, $-L^s-R'$, $-L^s-Si(R')_3$, $-L^s-OR'$, $-L^s-SR'$, $-L^s-N(R')_2$, $-O-L^s-R'$, $-O-L^s-Si(R)_3$, $-O-L^s-OR'$, $-O-L^s-SR'$, or $-O-L^s-N(R')_2$; wherein L^s is L^B as described herein, and each other variable is independently as described herein. In some embodiments, each of R^{1s} and R^{2s} is independently R^s. In some embodiments, R^s is −H. In some embodiments, R^s is not −H. In some embodiments, L^s is a covalent bond. In some embodiments, each of R^{2s} and R^{4s} are independently −H, −F, −OR, $-N(R)_2$. In some embodiments, R^{2s} is −H, −F, −OR, $-N(R)_2$. In some embodiments, R^{4s} is −H. In some embodiments, R^{2s} and R^{4s} form 2'$-O-L^s-$, wherein L^s is optionally substituted C_{1-6} alkylene. In some embodiments, L^s is optionally substituted $-CH_2-$. In some embodiments, L^s is optionally substituted $-CH_2-$.

[00764] In some embodiments, R is hydrogen. In some embodiments, R is not hydrogen. In some embodiments, R is an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-20} aryl, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclic ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00765] In some embodiments, R is optionally substituted C_{1-30} aliphatic. In some embodiments, R is optionally substituted C_{1-20} aliphatic. In some embodiments, R is optionally substituted C_{1-15} aliphatic. In some embodiments, R is optionally substituted C_{1-10} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted hexyl, pentyl, butyl, propyl, ethyl or methyl. In some embodiments, R is optionally substituted hexyl. In some embodiments, R is optionally substituted pentyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is optionally substituted propyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is hexyl. In some embodiments, R is pentyl. In some embodiments, R is butyl. In some embodiments, R is propyl. In some embodiments, R is ethyl. In some embodiments, R is methyl. In some embodiments, R is isopropyl. In some embodiments, R is n-propyl. In some embodiments, R is tert-butyl. In some embodiments, R is sec-butyl. In some embodiments, R is n-butyl. In some embodiments, R is $-(CH_2)_2OCH_3$.

[00766] In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

[00767] In some embodiments, R^{2s} is a 2'-modification as described in the present disclosure, and R^{4s} is −H. In some embodiments, R^{2s} is −OR, wherein R is not hydrogen. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −OMe. In some embodiments, R^{2s} is $-OCH_2CH_2CH_3$, e.g., in various X_{eo} utilized in Table 1 (X being m5C, T, G, A, etc.). In some embodiments, R^{2s} is selected from −H, −F, and −OR, wherein R is optionally substituted C_{1-6} alkl. In some embodiments, R^{2s} is selected from −H, −F, and −OMe.

[00768] In some embodiments, a sugar is a bicyclic sugar, e.g., sugars wherein R^{2s} and R^{4s} are taken to form

an optionally substituted ring as described in the present disclosure. In some embodiments, a sugar is selected from LNA sugars, BNA sugars, cEt sugars, etc. In some embodiments, a bridge is between the 2' and 4'-carbon atoms (corresponding to R^{2s} and R^{4s} taken together with their intervening atoms to form an optionally substituted ring as described herein). In some embodiments, a bridge is 2'–L^a–L^b–4', wherein L^a is –O–, –S– or N(R), and L^b is an optionally substituted C_{1-4} bivalent aliphatic chain, e.g., methylene.

[00769] In some embodiments, a sugar is a 2'-OMe, 2'-MOE, 2'-F, a LNA (locked nucleic acid) sugar, an ENA (ethylene bridged nucleic acid) sugar, a BNA(NMe) (Methylamino bridged nucleic acid) sugar, 2'-F ANA (2'-F arabinose), alpha-DNA (alpha-D-ribose), 2'/5' ODN (e.g., 2'/5' linked oligonucleotide), Inv (inverted sugar, e.g., inverted desoxyribose), AmR (Amino-Ribose), ThioR (Thio-ribose), HNA (hexose nucleic acid), CeNA (cyclohexene nucleic acid), or MOR (Morpholino) sugar.

[00770] Those skilled in the art after reading the present disclosure will appreciate that various types of sugar modifications are known and can be utilized in accordance with the present disclosure. In some embodiments, a sugar modification is a 2'-modification (e.g., R^{2s}). In some embodiments, a 2'-modification is 2'-F. In some embodiments, a 2'-modification is 2'-OR, wherein R is not hydrogen. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a 2'-modification is –O–L^b– or –L^b–L^b– which connects the 2'-carbon of a sugar moiety to another carbon of a sugar moiety. In some embodiments, a 2'-modification is 2'–O–L^b–4' or 2'–L^b–L^b–4' which connects the 2'-carbon of a sugar moiety to the 4'-carbon of a sugar moiety. In some embodiments, a 2'-modification is S-cEt. In some embodiments, a modified sugar is an LNA sugar. In some embodiments, –L^b– is –$C(R)_2$–. In some embodiments, a 2'-modification is (C2–O–$C(R)_2$–C4), wherein each R is independently as described in the present disclosure. In some embodiments, a 2'-modification is a LNA sugar modification (C2–O–CH_2–C4). In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is as described in the present disclosure. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, a 2'-modification is (C2–O–(*S*)-CHR–C4), wherein R is as described in the present disclosure and is not hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is unsubstituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2–O–CHR–C4), wherein R is ethyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-CHR–C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2–O–(*R*)-

CHR−C4), wherein R is ethyl. In some embodiments, a 2'-modification is (C2−O−(*S*)-CHR−C4), wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is (C2−O−(*S*)-CHR−C4), wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a 2'-modification is (C2−O−(*S*)-CHR−C4), wherein R is methyl. In some embodiments, a 2'-modification is (C2−O−(*S*)-CHR−C4), wherein R is ethyl. In some embodiments, a 2'-modification is C2−O−(*R*)-CH(CH_2CH_3)−C4. In some embodiments, a 2'-modification is C2−O−(*S*)-CH(CH_2CH_3)−C4. In some embodiments, a sugar is a natural DNA sugar. In some embodiments, a sugar is a natural RNA sugar. In some embodiments, a sugar is an optionally substituted natural DNA sugar. In some embodiments, a sugar is a natural DNA sugar optionally substituted at 2'. In some embodiments, a sugar is a natural DNA sugar substituted at 2' (2'-modification). In some embodiments, a sugar is a natural DNA sugar modified at 2' (2'-modification).

[00771] In some embodiments, a sugar is an optionally substituted ribose or deoxyribose. In some embodiments, a sugar is an optionally modified ribose or deoxyribose, wherein one or more hydroxyl groups of the ribose or deoxyribose moiety is optionally and independently replaced by halogen, R', $–N(R')_2$, –OR', or –SR', wherein each R' is as described herein. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with halogen, R', $–N(R')_2$, –OR', or –SR', wherein each R' is independently described in the present disclosure. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with halogen. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with one or more –F. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with –OR', wherein each R' is independently described in the present disclosure. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with –OR', wherein each R' is independently optionally substituted $C_1–C_6$ aliphatic. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with –OR', wherein each R' is independently an optionally substituted $C_1–C_6$ alkyl. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with –OMe. In some embodiments, a sugar is an optionally substituted deoxyribose, wherein the 2' position of the deoxyribose is optionally substituted with –O–methoxyethyl.

[00772] In some embodiments, provided oligonucleotides comprise one or more modified sugars. In some embodiments, provided oligonucleotides comprise one or more modified sugars and one or more natural sugars.

[00773] Examples of bicyclic sugars include sugars of alpha-L-methyleneoxy (4'-CH_2-O-2') LNA, beta-D-methyleneoxy (4'-CH_2-O-2') LNA, ethyleneoxy (4' -$(CH_2)_2$-O-2') LNA, aminooxy (4' -CH_2-O-N(R)-2') LNA, and oxyamino (4'-CH_2-N(R)-O-2') LNA. In some embodiments, a bicyclic sugar, e.g., a LNA or BNA sugar,

is sugar having at least one bridge between two sugar carbons. In some embodiments, a bicyclic sugar in a nucleoside may have the stereochemical configurations of alpha-L-ribofuranose or beta-D-ribofuranose.

[00774] In some embodiments, a bicyclic sugar may be further defined by isomeric configuration. For example, a sugar comprising a 4'-(CH_2)-O-2' bridge may be in the alpha-L configuration or in the beta-D configuration. In some embodiments, a 4' to 2' bridge is a -L-4'-(CH_2)-O-2', b-D-4'-CH_2-O-2', 4'-(CH_2)$_2$-O-2', 4'-CH_2-O-N(R')-2', 4'-CH_2-N(R')-O-2', 4'-CH(R')-O-2', 4'-CH(CH_3)-O-2', 4'-CH_2-S-2', 4'-CH_2-N(R')-2', 4'-CH_2-CH(R')-2', 4'-CH_2-CH(CH_3)-2', and 4'-(CH_2)$_3$-2', wherein each R' is as described in the present disclosure. In some embodiments, R' is −H, a protecting group or optionally substituted C_1-C_{12} alkyl. In some embodiments, R' is −H or optionally substituted C_1-C_{12} alkyl.

[00775] In some embodiments, a bicyclic sugar is a sugar of alpha-L-methyleneoxy (4'-CH_2-O-2') BNA, beta-D-methyleneoxy (4'-CH_2-O-2') BNA, ethyleneoxy (4'-(CH_2)$_2$-O-2') BNA, aminooxy (4'-CH_2-O-N(R)-2') BNA, oxyamino (4'-CH_2-N(R)-O-2') BNA, methyl(methyleneoxy) (4'-CH(CH_3)-O-2') BNA (also referred to as constrained ethyl or cEt), methylene-thio (4'-CH_2-S-2') BNA, methylene-amino (4'-CH_2-N(R)-2') BNA, methyl carbocyclic (4'-CH_2-CH(CH_3)-2') BNA, propylene carbocyclic (4'-(CH_2)$_3$-2') BNA, or vinyl BNA.

[00776] In some embodiments, a sugar modification is a modification described in US 9006198. In some embodiments, a modified sugar is described in US 9006198. In some embodiments, a sugar modification is a modification described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the sugar modifications and modified sugars of each of which are independently incorporated herein by reference.

[00777] In some embodiments a modified sugar is one described in US 5658873, US 5118800, US 5393878, US 5514785, US 5627053, US 7034133;7084125, US 7399845, US 5319080, US 5591722, US 5597909, US 5466786, US 6268490, US 6525191, US 5519134, US 5576427, US 6794499, US 6998484, US 7053207, US 4981957, US 5359044, US 6770748, US 7427672, US 5446137, US 6670461, US 7569686, US 7741457, US 8022193, US 8030467, US 8278425, US 5610300, US 5646265, US 8278426, US 5567811, US 5700920, US 8278283, US 5639873, US 5670633, US 8314227, US 2008/0039618, US 2009/0012281, WO 2021/030778, WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376.

[00778] In some embodiments, a sugar modification is 2'-OMe, 2'-MOE, 2'-LNA, 2'-F, 5'-vinyl, or S-cEt. In some embodiments, a modified sugar is a sugar of FRNA, FANA, or morpholino. In some embodiments, an oligonucleotide comprises a nucleic acid analog, e.g., GNA, LNA, PNA, TNA, F-HNA (F-THP or 3'-fluoro tetrahydropyran), MNA (mannitol nucleic acid, e.g., Leumann 2002 Bioorg. Med. Chem. 10: 841-854), ANA (anitol nucleic acid), or morpholino, or a portion thereof. In some embodiments, a sugar is as in flexible nucleic

acids or serinol nucleic acids. In some embodiments, a sugar modification replaces a natural sugar with another cyclic or acyclic moiety. Examples of such moieties are widely known in the art, e.g., those used in morpholino, glycol nucleic acids, etc. and may be utilized in accordance with the present disclosure. As appreciated by those skilled in the art, when utilized with modified sugars, in some embodiments internucleotidic linkages may be modified, e.g., as in morpholino, PNA, etc. In some embodiments, a sugar is a (R)-GNA sugar. In some embodiments, a sugar is a (S)-GNA sugar. In some embodiments, a nucleoside having a GNA sugar is utilized as N_{-1}, N_0 and/or N_1. In some embodiments, N_0 is a nucleoside having a GNA sugar. In some embodiments, a sugar is bicyclic sugar. In some embodiments, a sugar is a LNA sugar. In some embodiments, a sugar is an acyclic sugar. In some embodiments, a sugar is a UNA sugar. In some embodiments, a nucleoside having a UNA sugar is utilized as N_{-1}, N_0 and/or N_1. In some embodiments, N_0 is a nucleoside having a UNA sugar. In some embodiments, a nucleoside is abasic. In some embodiments, an abasic sugar is utilized as N_{-1}, N_0 and/or N_1. In some embodiments, N_0 is a nucleoside having an abasic sugar.

[00779] In some embodiments, a sugar is a 6'-modified bicyclic sugar that have either (R) or (S)-chirality at the 6-position, e.g., those described in US 7399845. In some embodiments, a sugar is a 5'-modified bicyclic sugar that has either (R) or (S)-chirality at the 5-position, e.g., those described in US 20070287831.

[00780] In some embodiments, a modified sugar contains one or more substituents at the 2' position (typically one substituent, and often at the axial position) independently selected from –F; $–CF_3$, –CN, $–N_3$, –NO, $–NO_2$, –OR', –SR', or $–N(R')_2$, wherein each R' is independently described in the present disclosure; $–O–(C_1–C_{10}$ alkyl), $–S–(C_1–C_{10}$ alkyl), $–NH–(C_1–C_{10}$ alkyl), or $–N(C_1–C_{10}$ alkyl)$_2$; $–O–(C_2–C_{10}$ alkenyl), $–S–(C_2–C_{10}$ alkenyl), $–NH–(C_2–C_{10}$ alkenyl), or $–N(C_2–C_{10}$ alkenyl)$_2$; $–O–(C_2–C_{10}$ alkynyl), $–S–(C_2–C_{10}$ alkynyl), $–NH–(C_2–C_{10}$ alkynyl), or $–N(C_2–C_{10}$ alkynyl)$_2$; or $–O––(C_1–C_{10}$ alkylene)$–O––(C_1–C_{10}$ alkyl), $–O–(C_1–C_{10}$ alkylene)–NH–($C_1–C_{10}$ alkyl) or $–O–(C_1–C_{10}$ alkylene)–NH($C_1–C_{10}$ alkyl)$_2$, –NH–($C_1–C_{10}$ alkylene)–O–($C_1–C_{10}$ alkyl), or $–N(C_1–C_{10}$ alkyl)–($C_1–C_{10}$ alkylene)–O–($C_1–C_{10}$ alkyl), wherein each of the alkyl, alkylene, alkenyl and alkynyl is independently and optionally substituted. In some embodiments, a substituent is $–O(CH_2)_nOCH_3$, $–O(CH_2)_nNH_2$, MOE, DMAOE, or DMAEOE, wherein wherein n is from 1 to about 10. In some embodiments, a modified sugar is one described in WO 2001/088198; and Martin et al., Helv. Chim. Acta, 1995, 78, 486-504. In some embodiments, a modified sugar comprises one or more groups selected from a substituted silyl group, an RNA cleaving group, a reporter group, a fluorescent label, an intercalator, a group for improving the pharmacokinetic properties of a nucleic acid, a group for improving the pharmacodynamic properties of a nucleic acid, or other substituents having similar properties. In some embodiments, modifications are made at one or more of the 2', 3', 4', or 5' positions, including the 3' position of the sugar on the 3'-terminal nucleoside or in the 5' position of the 5'-terminal nucleoside.

[00781] In some embodiments, the 2'-OH of a ribose is replaced with a group selected from –H, –F; $–CF_3$, –CN, $–N_3$, –NO, $–NO_2$, –OR', –SR', or $–N(R')_2$, wherein each R' is independently described in the present disclosure; $–O–(C_1–C_{10}$ alkyl), $–S–(C_1–C_{10}$ alkyl), $–NH–(C_1–C_{10}$ alkyl), or $–N(C_1–C_{10}$ alkyl)$_2$; $–O–(C_2–C_{10}$ alkenyl), $–S–(C_2–C_{10}$ alkenyl), $–NH–(C_2–C_{10}$ alkenyl), or $–N(C_2–C_{10}$ alkenyl)$_2$; $–O–(C_2–C_{10}$ alkynyl), $–S–(C_2–$

C_{10} alkynyl), –NH–(C_2–C_{10} alkynyl), or –N(C_2–C_{10} alkynyl)$_2$; or –O–(C_1–C_{10} alkylene)–O––(C_1–C_{10} alkyl), –O–(C_1–C_{10} alkylene)–NH–(C_1–C_{10} alkyl) or –O–(C_1–C_{10} alkylene)–NH(C_1–C_{10} alkyl)$_2$, –NH–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), wherein each of the alkyl, alkylene, alkenyl and alkynyl is independently and optionally substituted. In some embodiments, the 2'–OH is replaced with –H (deoxyribose). In some embodiments, the 2'–OH is replaced with –F. In some embodiments, the 2'–OH is replaced with –OR'. In some embodiments, the 2'–OH is replaced with –OMe. In some embodiments, the 2'–OH is replaced with –OCH_2CH_2OMe.

[00782] In some embodiments, a sugar modification is a 2'-modification. Commonly used 2'-modifications include but are not limited to 2'–OR, wherein R is not hydrogen and is as described in the present disclosure. In some embodiments, a modification is 2'–OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a modification is 2'–OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a modification is 2'–OMe. In some embodiments, a modification is 2'-MOE. In some embodiments, a 2'-modification is S-cEt. In some embodiments, a modified sugar is an LNA sugar. In some embodiments, a 2'-modification is –F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA. In some embodiments, a sugar modification is a 5'-modification, e.g., 5'-Me. In some embodiments, a sugar modification changes the size of the sugar ring. In some embodiments, a sugar modification is the sugar moiety in FHNA.

[00783] In some embodiments, a sugar modification replaces a sugar moiety with another cyclic or acyclic moiety. Examples of such moieties are widely known in the art, including but not limited to those used in morpholino (optionally with its phosphorodiamidate linkage), glycol nucleic acids, etc.

[00784] In some embodiments, one or more of the sugars of an oligonucleotide are modified. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, each modified sugar independently comprises a 2'-modification. In some embodiments, a 2'-modification is 2'-OR. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In some embodiments, a 2'-modification is an LNA sugar modification. In some embodiments, a 2'-modification is 2'-F. In some embodiments, each sugar modification is independently a 2'-modification. In some embodiments, each sugar modification is independently 2'-OR or 2'-F. In some embodiments, each sugar modification is independently 2'-OR or 2'-F, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, each sugar modification is independently 2'-OR or 2'-F, wherein at least one is 2'-F. In some embodiments, each sugar modification is independently 2'-OR or 2'-F, wherein R is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-OR. In some embodiments, each sugar modification is independently 2'-OR or 2'-F, wherein at least one is 2'-F, and at least one is 2'-OR. In some embodiments, each sugar modification is independently 2'-OR or 2'-F, wherein R is optionally substituted C_{1-6} alkyl, and wherein at least one is 2'-F, and at least one is 2'-OR. In some embodiments, each sugar modification is independently 2'-OR. In some embodiments, each sugar modification is independently 2'-OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, each sugar modification is 2'-OMe. In some embodiments, each

sugar modification is 2'-MOE. In some embodiments, each sugar modification is independently 2'-OMe or 2'-MOE. In some embodiments, each sugar modification is independently 2'-OMe, 2'-MOE, or a LNA sugar.

[00785] Modified sugars include cyclobutyl or cyclopentyl moieties in place of a pentofuranosyl sugar. Representative examples of such modified sugars include those described in US 4,981,957, US 5,118,800, US 5,319,080, or US 5,359,044. In some embodiments, the oxygen atom within the ribose ring is replaced by nitrogen, sulfur, selenium, or carbon. In some embodiments, −O− is replaced with −N(R')−, −S−, −Se− or $-C(R')_2-$. In some embodiments, a modified sugar is a modified ribose wherein the oxygen atom within the ribose ring is replaced with nitrogen, and wherein the nitrogen is optionally substituted with an alkyl group (e.g., methyl, ethyl, isopropyl, etc.).

[00786] A non-limiting example of modified sugars is glycerol, which is part of glycerol nucleic acids (GNAs), e.g., as described in Zhang, R et al., J. Am. Chem. Soc., 2008, 130, 5846-5847; Zhang L, et al., J. Am. Chem. Soc., 2005, 127, 4174-4175 and Tsai CH et al., PNAS, 2007, 14598-14603.

[00787] A flexible nucleic acid (FNA) is based on a mixed acetal aminal of formyl glycerol, e.g., as described in Joyce GF et al., PNAS, 1987, 84, 4398-4402 and Heuberger BD and Switzer C, J. Am. Chem. Soc., 2008, 130, 412-413.

[00788] In some embodiments, an oligonucleotide, and/or a modified nucleoside thereof, comprises a sugar or modified sugar described in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the sugars and modified sugars of each of which are independently incorporated herein by reference.

[00789] In some embodiments, one or more hydroxyl group in a sugar is optionally and independently replaced with halogen, R' $-N(R')_2$, –OR', or –SR', wherein each R' is independently described in the present disclosure.

[00790] In some embodiments, a modified nucleoside is any modified nucleoside described in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the modified nucleosides of each of which are independently incorporated herein by reference.

[00791] In some embodiments, a sugar modification is 5'-vinyl (R or S), 5'-methyl (R or S), 2'-SH, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F or 2'-$O(CH_2)_{20}CH_3$. In some embodiments, a substituent at the 2' position, e.g., a 2'-modification, is allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-$N(R_m)(R_n)$, O-CH_2-C(=O)-$N(R_m)(R_n)$, and O-CH_2-C(=O)-$N(R_1)$-$(CH_2)_2$-$N(R_m)(R_n)$, wherein each allyl, amino and alkyl is optionally substituted, and each of R_1, R_m and R_n is independently R' as described in the present disclosure. In some embodiments, each of R_1, R_m and R_n is independently −H or optionally substituted C_1-C_{10} alkyl.

[00792] In some embodiments, bicyclic sugars comprise a bridge, e.g., $-L^b-L^b-$, −L−, etc. between two sugar carbons, e.g., between the 4' and the 2' ribosyl ring carbon atoms. In some embodiments, a bridge is

4'−(CH_2)−O−2' (e.g., LNA sugars), 4'−(CH_2)−S−2', 4'−(CH_2)$_2$−O−2' (e.g., ENA sugars), 4'−CH(R')−O−2' (e.g., 4'−CH(CH_3)−O−2', 4'−CH(CH_2OCH_3)−O−2', and examples in US 7399845, etc.), 4'−CH(R')$_2$−O−2' (e.g., 4'−C(CH_3)(CH_3)−O−2' and examples in WO 2009006478, etc.), 4'-CH_2-N(OR')-2' (e.g., 4'-CH_2-N(OCH_3)-2', examples in WO 2008150729, etc.), 4'−CH_2−O−N(R')−2' (e.g., 4'−CH_2−O−N(CH_3)−2', examples in US 20040171570, etc.), 4'−CH_2−N(R')−O−2' [e.g., wherein R is −H, C_1-C_{12} alkyl, or a protecting group (e.g., see US 7427672)], 4'−C(R')$_2$−C(H)(R')−2' (e.g., 4'−CH_2−C(H)(CH_3)−2', examples in Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134, etc.), or 4'−C(R')$_2$−C(=C(R')$_2$)−2' (e.g., 4'−CH_2−C(=CH_2)−2', examples in WO 2008154401, etc.).

[00793] In some embodiments, a sugar is a tetrahydropyran or THP sugar. In some embodiments, a modified nucleoside is tetrahydropyran nucleoside or THP nucleoside which is a nucleoside having a six-membered tetrahydropyran sugar substituted for a pentofuranosyl residue in typical natural nucleosides. THP sugars and/or nucleosides include those used in hexitol nucleic acid (HNA), anitol nucleic acid (ANA), mannitol nucleic acid (MNA) (e.g., Leumann, Bioorg. Med. Chem., 2002, 10, 841-854) or fluoro HNA (F-HNA).

[00794] In some embodiments, sugars comprise rings having more than 5 atoms and/or more than one heteroatom, e.g., morpholino sugars which are described in e.g., Braasch et al., Biochemistry, 2002, 41, 4503-4510; US 5698685; US 5166315; US 5185444; US 5034506; etc.).

[00795] As those skilled in the art will appreciate, modifications of sugars, nucleobases, internucleotidic linkages, etc. can and are often utilized in combination in oligonucleotides, e.g., see various oligonucleotides in Table 1.

[00796] In some embodiments, a nucleoside has a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Example cyclohexenyl nucleosides and preparation and uses thereof are described in, e.g., WO 2010036696; Robeyns et al., J. Am. Chem. Soc., 2008, 130(6), 1979-1984; Horvath et al., Tetrahedron Letters, 2007, 48, 3621-3623; Nauwelaerts et al., J. Am. Chem. Soc., 2007, 129(30), 9340-9348; Gu et al., Nucleosides, Nucleotides & Nucleic Acids, 2005, 24(5-7), 993-998; Nauwelaerts et al., Nucleic Acids Research, 2005, 33(8), 2452-2463; Robeyns et al., Acta Crystallographica, Section F: Structural Biology and Crystallization Communications, 2005, F61(6), 585-586; Gu et al., Tetrahedron, 2004, 60(9), 2111-2123; Gu et al., Oligonucleotides, 2003, 13(6), 479-489; Wang et al., J. Org. Chem., 2003, 68, 4499-4505; Verbeure et al., Nucleic Acids Research, 2001, 29(24), 4941-4947; Wang et al., J. Org. Chem., 2001, 66, 8478-82; Wang et al., Nucleosides, Nucleotides & Nucleic Acids, 2001, 20(4-7), 785-788; Wang et al., J. Am. Chem., 2000, 122, 8595-8602; WO 2006047842; WO 2001049687; etc.

[00797] Many monocyclic, bicyclic and tricyclic ring systems are suitable as sugar surrogates (modified sugars) and may be utilized in accordance with the present disclosure. See, e.g., Leumann, Christian J. Bioorg. & Med. Chem., 2002, 10, 841-854. Such ring systems can undergo various additional substitutions to further enhance their properties and/or activities.

[00798] In some embodiments, a 2'-modified sugar is a furanosyl sugar modified at the 2' position. In some embodiments, a 2'-modification is halogen, −R' (wherein R' is not −H), −OR' (wherein R' is not −H), −SR',

$-N(R')_2$, optionally substituted $-CH_2-CH=CH_2$, optionally substituted alkenyl, or optionally substituted alkynyl. In some embodiments, a 2'-modifications is selected from $-O[(CH_2)_nO]_mCH_3$, $-O(CH_2)_nNH_2$, $-O(CH_2)_nCH_3$, $-O(CH_2)_nF$, $-O(CH_2)_nONH_2$, $-OCH_2C(=O)N(H)CH_3$, and $-O(CH_2)_nON[(CH_2)_nCH_3]_2$, wherein each n and m is independently from 1 to about 10. In some embodiments, a 2'-modification is optionally substituted C_1-C_{12} alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted $-O-$alkaryl, optionally substituted $-O-$aralkyl, $-SH$, $-SCH_3$, $-OCN$, $-Cl$, $-Br$, $-CN$, $-F$, $-CF_3$, $-OCF_3$, $-SOCH_3$, $-SO_2CH_3$, $-ONO_2$, $-NO_2$, $-N_3$, $-NH_2$, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkaryl, optionally substituted aminoalkylamino, optionally substituted polyalkylamino, substituted silyl, a reporter group, an intercalator, a group for improving pharmacokinetic properties, a group for improving the pharmacodynamic properties, and other substituents. In some embodiments, a 2'-modification is a 2'-MOE modification (e.g., see Baker et al., J. Biol. Chem., 1997, 272, 11944-12000). In some cases, a 2'-MOE modification has been reported as having improved binding affinity compared to unmodified sugars and to some other modified nucleosides, such as 2'- O-methyl, 2'-O-propyl, and 2'-O-aminopropyl. Oligonucleotides having the 2'-MOE modification have also been reported to be capable of inhibiting gene expression with promising features for in vivo use (see, e.g., Martin, Helv. Chim. Acta, 1995, 78, 486-504; Altmann et al., Chimia, 1996, 50, 168-176; Altmann et al., Biochem. Soc. Trans., 1996, 24, 630-637; and Altmann et al., Nucleosides Nucleotides, 1997, 16, 917-926; etc.).

[00799] In some embodiments, a 2'-modified or 2'-substituted sugar or nucleoside is a sugar or nucleoside comprising a substituent at the 2' position of the sugar which is other than $-H$ (typically not considered a substituent) or $-OH$. In some embodiments, a 2'-modified sugar is a bicyclic sugar comprising a bridge connecting two carbon atoms of the sugar ring one of which is the 2' carbon. In some embodiments, a 2'-modification is non-bridging, e.g., allyl, amino, azido, thio, optionally substituted $-O-$allyl, optionally substituted $-O-C_1$-C_{10} alkyl, $-OCF_3$, $-O(CH_2)_2OCH_3$, 2'-$O(CH_2)_2SCH_3$, $-O(CH_2)_2ON(R_m)(R_n)$, or $-OCH_2C(=O)N(R_m)(R_n)$, where each R_m and R_n is independently $-H$ or optionally substituted C_1-C_{10} alkyl.

[00800] Certain modified sugars, their preparation and uses are described in US 4981957, US 5118800, US 5319080, US 5359044, US 5393878, US 5446137, US 5466786, US 5514785, US 5519134, US 5567811, US 5576427, US 5591722, US 5597909, US 5610300, US 5627053, US 5639873, US 5646265, US 5670633, US 5700920, US 5792847, US 6600032 and WO 2005121371.

[00801] In some embodiments, a sugar is the sugar of N-methanocarba, LNA, cMOE BNA, cEt BNA, α-L-LNA or related analogs, HNA, Me-ANA, MOE-ANA, Ara-FHNA, FHNA, R-6'-Me-FHNA, S-6'-Me-FHNA, ENA, or c-ANA. In some embodiments, a modified internucleotidic linkage is C3-amide (e.g., sugar that has the amide modification attached to the C3', Mutisya et al. 2014 Nucleic Acids Res. 2014 Jun 1; 42(10): 6542–6551), formacetal, thioformacetal, MMI [e.g., methylene(methylimino), Peoc'h et al. 2006 Nucleosides and Nucleotides 16 (7-9)], a PMO (phosphorodiamidate linked morpholino) linkage (which connects two sugars),

or a PNA (peptide nucleic acid) linkage. In some embodiments, examples of internucleotidic linkages and/or sugars are described in Allerson et al. 2005 J. Med. Chem. 48: 901-4; BMCL 2011 21: 1122; BMCL 2011 21: 588; BMCL 2012 22: 296; Chattopadhyaya et al. 2007 J. Am. Chem. Soc. 129: 8362; Chem. Bio. Chem. 2013 14: 58; Curr. Prot. Nucl. Acids Chem. 2011 1.24.1; Egli et al. 2011 J. Am. Chem. Soc. 133: 16642; Hendrix et al. 1997 Chem. Eur. J. 3: 110; Hyrup et al. 1996 Bioorg. Med. Chem. 4: 5; Imanishi 1997 Tet. Lett. 38: 8735; J. Am. Chem. Soc. 1994, 116, 3143; J. Med. Chem. 2009 52: 10; J. Org. Chem. 2010 75: 1589; Jepsen et al. 2004 Oligo. 14: 130-146; Jones et al. J. Org. Chem. 1993, 58, 2983; Jung et al. 2014 ACIEE 53: 9893; Kodama et al. 2014 AGDS; Koizumi 2003 BMC 11: 2211; Koizumi et al. 2003 Nuc. Acids Res. 12: 3267-3273; Koshkin et al. 1998 Tetrahedron 54: 3607-3630; Kumar et al. 1998 Bioo. Med. Chem. Let. 8: 2219-2222; Lauritsen et al. 2002 Chem. Comm. 5: 530-531; Lauritsen et al. 2003 Bioo. Med. Chem. Lett. 13: 253-256; Lima et al. 2012 Cell 150: 883-894; Mesmaeker et al. Angew. Chem., Int. Ed. Engl. 1994, 33, 226; Migawa et al. 2013 Org. Lett. 15: 4316; Mol. Ther. Nucl. Acids 2012 1: e47; Morita et al. 2001 Nucl. Acids Res. Supp. 1: 241-242; Morita et al. 2002 Bioo. Med. Chem. Lett. 12: 73-76; Morita et al. 2003 Bioo. Med. Chem. Lett. 2211-2226; Murray et al. 2012 Nucl. Acids Res. 40: 6135; Nielsen et al. 1997 Chem. Soc. Rev. 73; Nielsen et al. 1997 J. Chem. Soc. Perkins Transl. 1: 3423-3433; Obika et al. 1997 Tetrahedron Lett. 38 (50): 8735–8; Obika et al. 1998 Tetrahedron Lett. 39: 5401-5404; Obika et al. 2008 J. Am. Chem. Soc. 130: 4886; Obika et al. 2011 Org. Lett. 13: 6050; Oestergaard et al. 2014 JOC 79: 8877; Pallan et al. 2012 Biochem. 51: 7; Pallan et al. 2012 Chem. Comm. 48: 8195-8197; Petersen et al. 2003 TRENDS Biotech. 21: 74-81; Prakash et al. 2010 J. Med. Chem. 53: 1636; Prakash et al. 2015 Nucl. Acids Res. 43: 2993-3011; Prakash et al. 2016 Bioorg. Med. Chem. Lett. 26: 2817-2820; Rajwanshi et al. 1999 Chem. Commun. 1395-1396; Schultz et al. 1996 Nucleic Acids Res. 24: 2966; Seth et al. 2008 Nucl. Acid Sym. Ser. 52: 553; Seth et al. 2009 J. Med. Chem. 52: 10-13; Seth et al. 2010 J. Am. Chem. Soc. 132: 14942; Seth et al. 2010 J. Med. Chem. 53: 8309-8318; Seth et al. 2010 J. Org. Chem. 75: 1569-1581; Seth et al. 2011 BMCL 21: 4690; Seth et al. 2012 Bioo. Med. Chem. Lett. 22: 296-299; Seth et al. 2012 Mol. Ther-Nuc. Acids. 1, e47; Seth et al., Nucleic Acids Symposium Series (2008), 52(1), 553-554; Singh et al. 1998 Chem. Comm. 1247-1248; Singh et al. 1998 J. Org. Chem. 63: 10035-39; Singh et al. 1998 J. Org. Chem. 63: 6078-6079; Sorensen 2003 Chem. Comm. 2130-2131; Starrup et al. 2010 Nucl. Acids Res. 38: 7100; Swayze et al. 2007 Nucl. Acids Res. 35: 687; Ts'o et al. Ann. N. Y. Acad. Sci. 1988, 507, 220; Van Aerschot et al. 1995 Angew. Chem. Int. Ed. Engl. 34: 1338; Vasseur et al. J. Am. Chem. Soc. 1992, 114, 4006; WO 2007090071; WO 2016079181; US 6326199; US 6066500; or US 6440739.

[00802] In some embodiments, an oligonucleotide or a portion thereof (e.g., a domain, a subdomain, etc.) comprise a high level of 2'-F modified sugars, e.g., about 10%-100% (e.g., about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, or about 100%) of sugars in an oligonucleotide or a portion thereof (e.g., a domain, a subdomain, etc.) comprises 2'-F. In some embodiments, about 50% or more of sugars in an oligonucleotide or a portion thereof comprises 2'-F. In some embodiments, about 60% or more of sugars in an oligonucleotide or a portion thereof comprises 2'-F. In some embodiments,

about 70% or more of sugars in an oligonucleotide or a portion thereof comprises 2'-F. In some embodiments, about 80% or more of sugars in an oligonucleotide or a portion thereof comprises 2'-F. In some embodiments, about 90% or more of sugars in an oligonucleotide or a portion thereof comprises 2'-F. In some embodiments, an oligonucleotide or a portion thereof also comprises one or more sugars comprising no 2'-F (e.g., sugars comprising no modifications and/or sugars comprising other modifications).

[00803] In some embodiments, no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in an oligonucleotide or a portion thereof (e.g., a domain, a subdomain, etc.) comprises 2'-MOE. In some embodiments, no more than about 50% of sugars in an oligonucleotide or a portion thereof comprises 2'-MOE. In some embodiments, no sugars in an oligonucleotide or a portion thereof comprises 2'-MOE. In some embodiments, no more than 1, 2, 3, 4, or 5 sugars in an oligonucleotide or a portion thereof comprises 2'-MOE.

[00804] Various additional sugars useful for preparing oligonucleotides or analogs thereof are known in the art and may be utilized in accordance with the present disclosure.

Internucleotidic linkages

[00805] Among other things, the present disclosure provides various internucleotidic linkages, including various modified internucleotidic linkages, that may be utilized together with other structural elements, e.g., various sugars as described herein, to provide oligonucleotides and compositions thereof.

[00806] In some embodiments, oligonucleotides comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications. Various internucleotidic linkages can be utilized in accordance with the present disclosure to link units comprising nucleobases, e.g., nucleosides. In some embodiments, provided oligonucleotides comprise both one or more modified internucleotidic linkages and one or more natural phosphate linkages. As widely known by those skilled in the art, natural phosphate linkages are widely found in natural DNA and RNA molecules; they have the structure of $-OP(O)(OH)O-$, connect sugars in the nucleosides in DNA and RNA, and may be in various salt forms, for example, at physiological pH (about 7.4), natural phosphate linkages are predominantly exist in salt forms with the anion being $-OP(O)(O^-)O-$. A modified internucleotidic linkage, or a non-natural phosphate linkage, is an internucleotidic linkage that is not natural phosphate linkage or a salt form thereof. Modified internucleotidic linkages, depending on their structures, may also be in their salt forms. For example, as appreciated by those skilled in the art, phosphorothioate internucleotidic linkages which have the structure of $-OP(O)(SH)O-$ may be in various salt forms, e.g., at physiological pH (about 7.4) with the anion being $-OP(O)(S^-)O-$.

[00807] In some embodiments, an oligonucleotide comprises an internucleotidic linkage which is a modified internucleotidic linkage, e.g., phosphorothioate, phosphorodithioate, methylphosphonate, phosphoroamidate, thiophosphate, 3'-thiophosphate, or 5'-thiophosphate.

[00808] In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage which

comprises a chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled with respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is stereochemically pure with respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is not chirally controlled. In some embodiments, a pattern of backbone chiral centers comprises or consists of positions and linkage phosphorus configurations of chirally controlled internucleotidic linkages (*R*p or *S*p) and positions of achiral internucleotidic linkages (e.g., natural phosphate linkages).

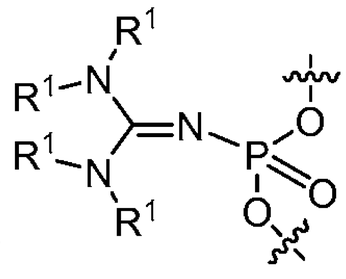
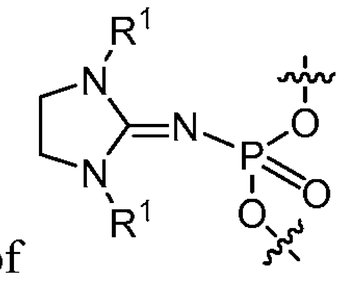
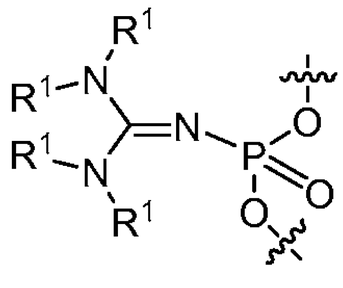
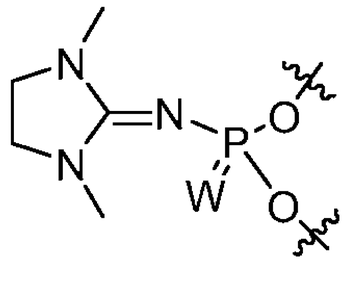
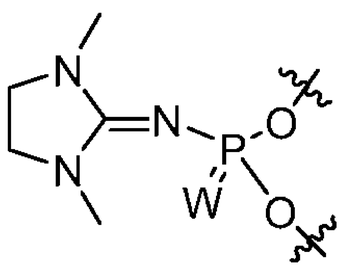
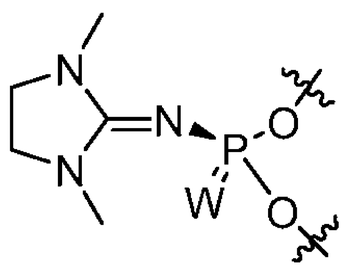
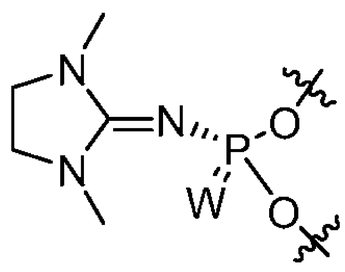
[00809] In some embodiments, an internucleotidic linkage comprises a P-modification, wherein a P-modification is a modification at a linkage phosphorus. In some embodiments, a modified internucleotidic linkage is a moiety which does not comprise a phosphorus but serves to link two sugars or two moieties that each independently comprises a nucleobase, e.g., as in peptide nucleic acid (PNA).

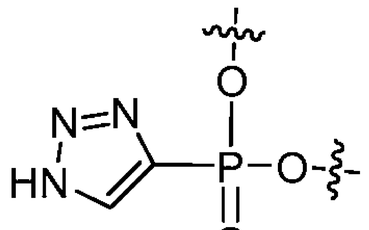
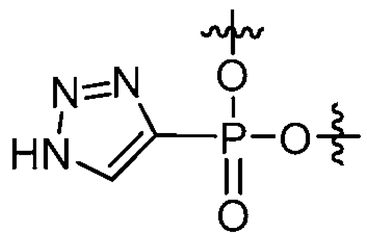
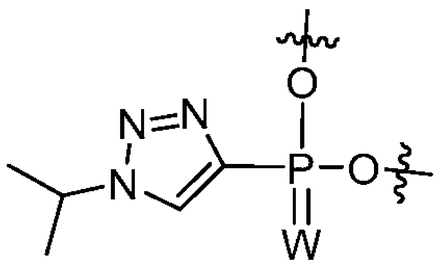
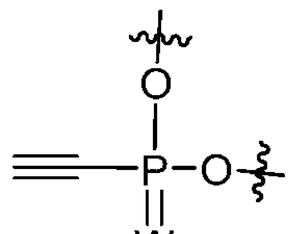
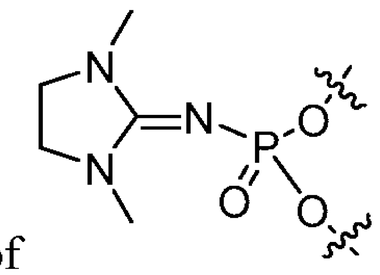
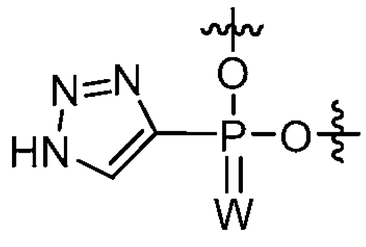
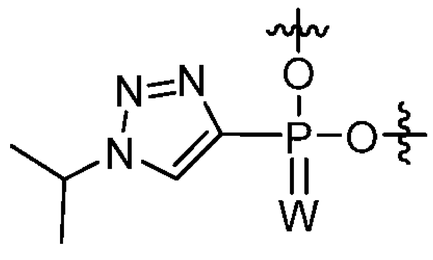
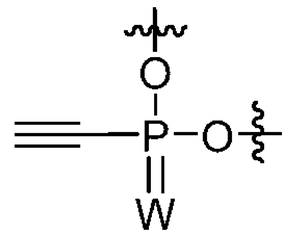
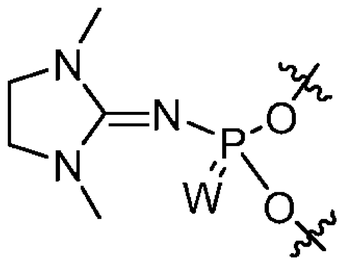
[00810] In some embodiments, an oligonucleotide comprises a modified internucleotidic linkage, e.g., those having the structure of Formula **I**, **I-a**, **I-b**, or **I-c** and described herein and/or in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the internucleotidic linkages (e.g., those of Formula **I**, **I-a**, **I-b**, **I-c**, etc.) of each of which are independently incorporated herein by reference. In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

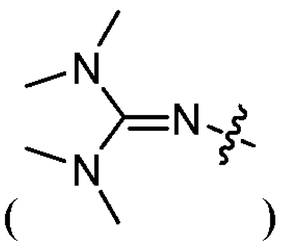
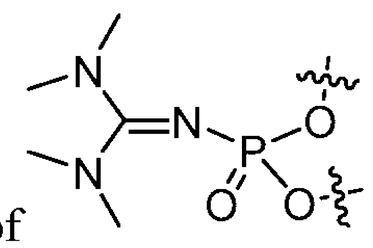
[00811] In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, the present disclosure provides oligonucleotides comprising one or more neutral internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage has the structure of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof, as described herein and/or in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the non-negatively charged internucleotidic linkages (e.g., those of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a suitable salt form thereof) of each of which are independently incorporated

herein by reference.

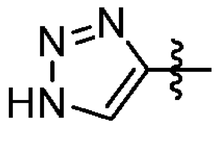
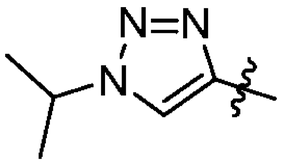
[00812] In some embodiments, a non-negatively charged internucleotidic linkage can improve the delivery and/or activities (e.g., adenosine editing activity).

[00813] In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted triazolyl. In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted alkynyl. In some embodiments, a modified internucleotidic linkage comprises a triazole or alkyne moiety. In some embodiments, a triazole moiety, e.g., a triazolyl group, is optionally substituted. In some embodiments, a triazole moiety, e.g., a triazolyl group) is substituted. In some embodiments, a triazole moiety is unsubstituted. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety. In some embodiments, a modified internucleotidic linkage has the structure of  and is optionally chirally controlled, wherein R^1 is −L−R', wherein L is L^B as described herein, and R' is as described herein. In some embodiments, each R^1 is independently R'. In some embodiments, each R' is independently R. In some embodiments, two R^1 are R and are taken together to form a ring as described herein. In some embodiments, two R^1 on two different nitrogen atoms are R and are taken together to form a ring as described herein. In some embodiments, R^1 is independently optionally substituted C_{1-6} aliphatic as described herein. In some embodiments, R^1 is methyl. In some embodiments, two R' on the same nitrogen atom are R and are taken together to form a ring as described herein. In some embodiments, a modified internucleotidic linkage has the structure of  and is optionally chirally controlled. In some embodiments,  is  . In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety and has the structure of:  ,  , or  , wherein W is O or S. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

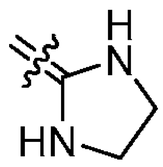
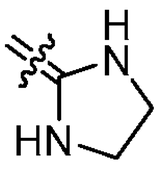
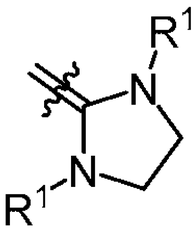
[00814] In some embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage is an internucleotidic linkage comprising a triazole moiety. In some embodiments, a non-negatively charged internucleotidic linkage or a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the formula of  , where W is O or S. In some embodiments, an internucleotidic linkage comprising an alkyne moiety (e.g., an optionally substituted alkynyl group) has the formula of  , wherein W is O or S. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure selected from  ,  ,  , or  , wherein W is O or S.

[00815] In some embodiments, an internucleotidic linkage comprises a Tmg group (). In some embodiments, an internucleotidic linkage comprises a Tmg group and has the structure of  (the "Tmg internucleotidic linkage"). In some embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and an Tmg internucleotidic linkage.

[00816] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, such a heterocyclyl or heteroaryl group is of a 5-membered ring. In some embodiments, such a heterocyclyl or heteroaryl group is of a 6-membered ring.

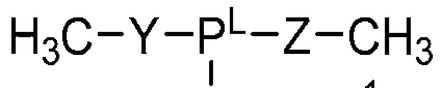
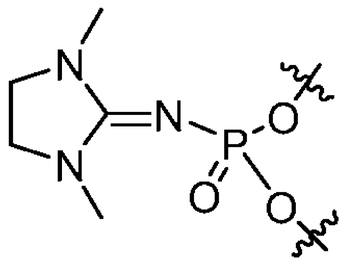
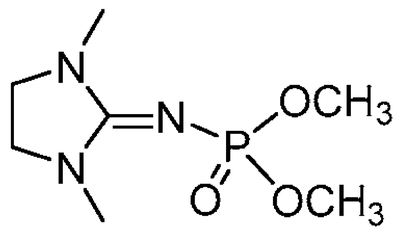
[00817] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a heteroaryl group is directly bonded to a linkage phosphorus. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an unsubstituted triazolyl group, e.g.,  . In some embodiments, a non-negatively charged internucleotidic linkage comprises a substituted triazolyl group, e.g.,  .

[00818] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl

group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, at least two heteroatoms are nitrogen. In some embodiments, a heterocyclyl group is directly bonded to a linkage phosphorus. In some embodiments, a heterocyclyl group is bonded to a linkage phosphorus through a linker, e.g., =N− when the heterocyclyl group is part of a guanidine moiety who directed bonded to a linkage phosphorus through its =N−. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises a  group, wherein each R^1 is independently −L−R. In some embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R^1 is independently methyl.

[00819] In some embodiments, a modified internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, comprises a triazole or alkyne moiety, each of which is optionally substituted. In some embodiments, a modified internucleotidic linkage comprises a triazole moiety. In some embodiments, a modified internucleotidic linkage comprises a unsubstituted triazole moiety. In some embodiments, a modified internucleotidic linkage comprises a substituted triazole moiety. In some embodiments, a modified internucleotidic linkage comprises an alkyl moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted alkynyl group. In some embodiments, a modified internucleotidic linkage comprises an unsubstituted alkynyl group. In some embodiments, a modified internucleotidic linkage comprises a substituted alkynyl group. In some embodiments, an alkynyl group is directly bonded to a linkage phosphorus.

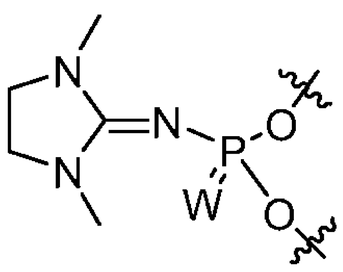
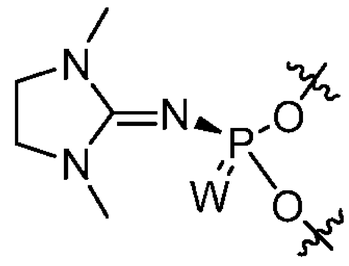
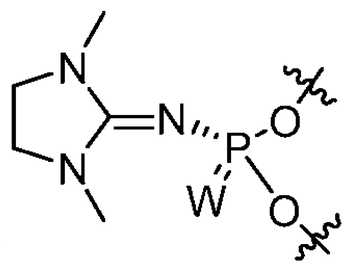
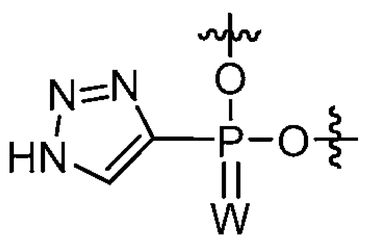
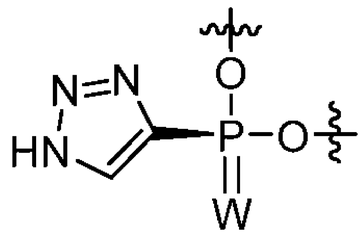
[00820] In some embodiments, an oligonucleotide comprises different types of internucleotidic phosphorus linkages. In some embodiments, a chirally controlled oligonucleotide comprises at least one natural phosphate linkage and at least one modified (non-natural) internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one natural phosphate linkage and at least one phosphorothioate. In some embodiments, an oligonucleotide comprises at least one non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one natural phosphate linkage and at least one non-

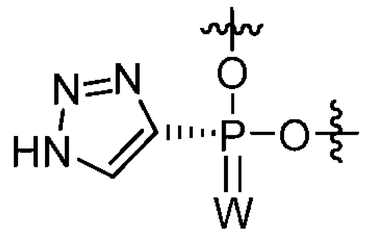
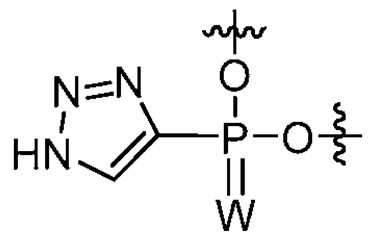
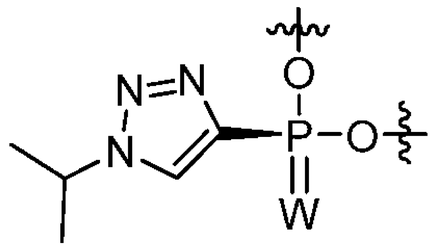
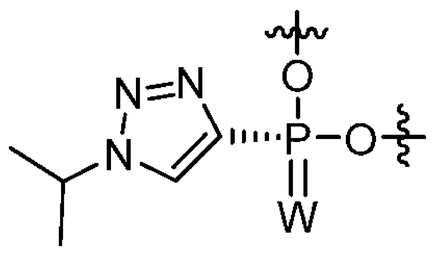
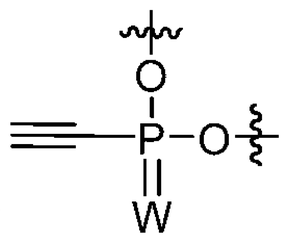
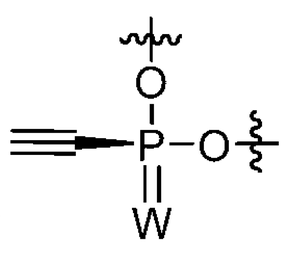
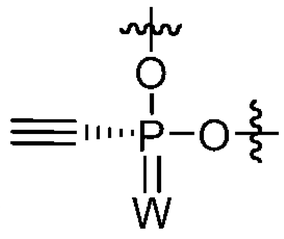
negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one phosphorothioate internucleotidic linkage and at least one non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least one phosphorothioate internucleotidic linkage, at least one natural phosphate linkage, and at least one non-negatively charged internucleotidic linkage. In some embodiments, oligonucleotides comprise one or more, e.g., 1-50, 1-40, 1-30, 1-20, 1-15, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more non-negatively charged internucleotidic linkages. In some embodiments, oligonucleotides comprise no more than a certain number of non-negatively charged internucleotidic linkages, e.g., no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, no more than 6, no more than 7, no more than 8, no more than 9, no more than 10, no more than 11, no more than 12, no more than 13, no more than 14, no more than 15, no more than 16, no more than 17, no more than 18, no more than 19, no more than 20, no more than 21, no more than 22, no more than 23, no more than 24, no more than 25, no more than 26, no more than 27, no more than 28, no more than 29, or no more than 30 non-negatively charged internucleotidic linkages. In some embodiments, oligonucleotides comprise no non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is not negatively charged in that at a given pH in an aqueous solution less than 50%, 40%, 40%, 30%, 20%, 10%, 5%, or 1% of the internucleotidic linkage exists in a negatively charged salt form. In some embodiments, a pH is about pH 7.4. In some embodiments, a pH is about 4-9. In some embodiments, the percentage is less than 10%. In some embodiments, the percentage is less than 5%. In some embodiments, the percentage is less than 1%. In some embodiments, an internucleotidic linkage is a non-negatively charged internucleotidic linkage in that the neutral form of the internucleotidic linkage has no pKa that is no more than about 1, 2, 3, 4, 5, 6, or 7 in water. In some embodiments, no pKa is 7 or less. In some embodiments, no pKa is 6 or less. In some embodiments, no pKa is 5 or less. In some embodiments, no pKa is 4 or less. In some embodiments, no pKa is 3 or less. In some embodiments, no pKa is 2 or less. In some embodiments, no pKa is 1 or less. In some embodiments, pKa of the neutral form of an internucleotidic linkage can be represented by pKa of the neutral form of a compound having the structure of CH_3–the internucleotidic linkage–CH_3. For example, pKa of the neutral form of an internucleotidic linkage having the structure of Formula I may be represented by the pKa of the neutral form of a compound having the structure of  (wherein each of X, Y, Z is independently –O–, –S–, –N(R')–; L is L^B, and R^1 is –L–R'), pKa of  can be represented by pKa  . In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a positively-charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage comprises a guanidine moiety. In some embodiments, a non-

negatively charged internucleotidic linkage comprises a heteroaryl base moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises a triazole moiety. In some embodiments, a non-negatively charged internucleotidic linkage comprises an alkynyl moiety.

[00821] In some embodiments, a neutral or non-negatively charged internucleotidic linkage has the structure of any neutral or non-negatively charged internucleotidic linkage described in any of: US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, each neutral or non-negatively charged internucleotidic linkage of each of which is hereby incorporated by reference.

[00822] In some embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R' is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R' is independently $-CH_3$. In some embodiments, each R^s is $-H$.

[00823] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic

linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a neutral internucleotidic linkage is a non-negatively charged internucleotidic linkage described above.

[00824] In some embodiments, provided oligonucleotides comprise 1 or more internucleotidic linkages of Formula **I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1,** or **II-d-2**, which are described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the Formula **I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1,** or **II-d-2**, or salt forms thereof, each of which are independently incorporated herein by

reference.

[00825] In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage which is not the neutral internucleotidic linkage. In some embodiments, an oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled phosphorothioate internucleotidic linkage. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more non-negatively charged internucleotidic linkages and one or more phosphorothioate internucleotidic linkages, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more neutral internucleotidic linkages and one or more phosphorothioate internucleotidic linkage, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, an oligonucleotide comprises at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more chirally controlled phosphorothioate internucleotidic linkages. In some embodiments, non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a neutral internucleotidic linkage is chirally controlled. In some embodiments, a neutral internucleotidic linkage is not chirally controlled. In some embodiments, an oligonucleotide comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) chirally controlled and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled chiral internucleotidic linkages. In some embodiments, an oligonucleotide comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) chirally controlled and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled non-negatively charged internucleotidic linkages (in some embodiments, each of which is independently n001). In some embodiments, a neutral internucleotidic linkage is chirally controlled. In some embodiments, a neutral internucleotidic linkage is not chirally controlled. In some embodiments, an oligonucleotide comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) chirally controlled and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) non-chirally controlled neutral internucleotidic linkages (in some embodiments, each of which is independently n001).

[00826] Without wishing to be bound by any particular theory, the present disclosure notes that a neutral internucleotidic linkage can be more hydrophobic than a phosphorothioate internucleotidic linkage (PS), which can be more hydrophobic than a natural phosphate linkage (PO). Typically, unlike a PS or PO, a neutral internucleotidic linkage bears less charge. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages into an oligonucleotide may increase oligonucleotides' ability to be taken up by a cell and/or to escape from endosomes. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages can be utilized to modulate melting temperature of duplexes formed between an oligonucleotide and its target nucleic acid.

[00827] Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into an oligonucleotide may be able to increase the oligonucleotide's ability to mediate a function such as target adenosine editing.

[00828] As appreciated by those skilled in the art, internucleotidic linkages such as natural phosphate linkages and those of Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt forms thereof typically connect two nucleosides (which can either be natural or modified) as described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt forms thereof, each of which are independently incorporated herein by reference. A typical connection, as in natural DNA and RNA, is that an internucleotidic linkage forms bonds with two sugars (which can be either unmodified or modified as described herein). In many embodiments, as exemplified herein an internucleotidic linkage forms bonds through its oxygen atoms or heteroatoms (e.g., Y and Z in various formulae) with one optionally modified ribose or deoxyribose at its 5' carbon, and the other optionally modified ribose or deoxyribose at its 3' carbon. In some embodiments, each nucleoside units connected by an internucleotidic linkage independently comprises a nucleobase which is independently an optionally substituted A, T, C, G, or U, or a substituted tautomer of A, T, C, G or U, or a nucleobase comprising an optionally substituted heterocyclyl and/or a heteroaryl ring having at least one nitrogen atom.

[00829] In some embodiments, a linkage has the structure of or comprises $-Y-P^L(-X-R^L)-Z-$, or a salt form thereof, wherein:

P^L is P, P(=W), $P->B(-L^L-R^L)_3$, or P^N;

W is O, $N(-L^L-R^L)$, S or Se;

P^N is $P=N-C(-L^L-R')(=L^N-R')$ or $P=N-L^L-R^L$;

L^N is $=N-L^{L1}-$, $=CH-L^{L1}-$ wherein CH is optionally substituted, or $=N^+(R')(Q^-)-L^{L1}-$;

Q^- is an anion;

each of X, Y and Z is independently –O–, –S–, $-L^L-N(-L^L-R^L)-L^L-$, $-L^L-N=C(-L^L-R^L)-L^L-$, or L^L;

each R^L is independently $-L^L-N(R')_2$, $-L^L-R'$, $-N=C(-L^L-R')_2$, $-L^L-N(R')C(NR')N(R')_2$, $-L^L-N(R')C(O)N(R')_2$, a carbohydrate, or one or more additional chemical moieties optionally connected through a linker;

each of L^{L1} and L^L is independently L;

$-Cy^{IL}-$ is $-Cy-$;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(NR')N(R')−, −N(R')C(NR')N(R')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, $-P(OR')[B(R')_3]-$, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, $-OP(OR')[B(R')_3]O-$, and $-[C(R')_2C(R')_2O]n-$, wherein n is 1-50, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent 3-30 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each Cy^L is independently an optionally substituted trivalent or tetravalent, 3-30 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R' is independently −R, −C(O)R, $-C(O)N(R)_2$, −C(O)OR, or $-S(O)_2R$;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00830] In some embodiments, an internucleotidic linkage has the structure of $-O-P^L(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N(-L^L-R^L)-R^L]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-NH-L^L-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N(R')_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the

structure of −O−P(=W)(−NHR')−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −O−P(=W)(−$NHSO_2R$)−O−, wherein each variable is independently as described herein. In some embodiments, R is methyl. In some embodiments, an internucleotidic linkage is −O−P(=O)(−$NHSO_2CH_3$)−O−. In some embodiments, an internucleotidic linkage has the structure of −O−P(=W)[−N=C(–L^L–R')$_2$]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −O−P(=W)[−N=C[N(R')$_2$]$_2$]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=W)(−N=C(R")$_2$)−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=W)(−N(R")$_2$)−O−, wherein each variable is independently as described herein. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, such an internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, such an internucleotidic linkage is a neutral internucleotidic linkage.

[00831] In some embodiments, an internucleotidic linkage has the structure of −P^L(−X−R^L)−Z−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P^L(−X−R^L)−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−X−R^L)−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)[−N(–L^L–R^L)−R^L]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−NH–L^L–R^L)−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)[−N(R')$_2$]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−NHR')−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−$NHSO_2R$)−O−, wherein each variable is independently as described herein. In some embodiments, R is methyl. In some embodiments, an internucleotidic linkage is −P(=O)(−$NHSO_2CH_3$)−O−. In some embodiments, an internucleotidic linkage has the structure of −P(=W)[−N=C(–L^L–R')$_2$]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)[−N=C[N(R')$_2$]$_2$]−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−N=C(R")$_2$)−O−, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=W)(−N(R")$_2$)−O−, wherein each variable is independently as described herein. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, such an internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, such an internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, P of such an internucleotidic linkage is bonded to N of a sugar.

[00832] In some embodiments, a linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a linkage is a thio-phosphoryl guanidine internucleotidic linkage.

[00833] In some embodiments, one or more methylene units are optionally and independently replaced with a moiety as described herein. In some embodiments, L or L^L is or comprises $-SO_2-$. In some embodiments, L or L^L is or comprises $-SO_2N(R')-$. In some embodiments, L or L^L is or comprises $-C(O)-$. In some embodiments, L or L^L is or comprises $-C(O)O-$. In some embodiments, L or L^L is or comprises $-C(O)N(R')-$. In some embodiments, L or L^L is or comprises $-P(=W)(R')-$. In some embodiments, L or L^L is or comprises $-P(=O)(R')-$. In some embodiments, L or L^L is or comprises $-P(=S)(R')-$. In some embodiments, L or L^L is or comprises $-P(R')-$. In some embodiments, L or L^L is or comprises $-P(=W)(OR')-$. In some embodiments, L or L^L is or comprises $-P(=O)(OR')-$. In some embodiments, L or L^L is or comprises $-P(=S)(OR')-$. In some embodiments, L or L^L is or comprises $-P(OR')-$.

[00834] In some embodiments, $-X-R^L$ is $-N(R')SO_2R^L$. In some embodiments, $-X-R^L$ is $-N(R')C(O)R^L$. In some embodiments, $-X-R^L$ is $-N(R')P(=O)(R')R^L$.

[00835] In some embodiments, a linkage, e.g., a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage, has the structure of or comprises $-P(=W)(-N=C(R'')_2)-$, $-P(=W)(-N(R')SO_2R'')-$, $-P(=W)(-N(R')C(O)R'')-$, $-P(=W)(-N(R'')_2)-$, $-P(=W)(-N(R')P(O)(R'')_2)-$, $-OP(=W)(-N=C(R'')_2)O-$, $-OP(=W)(-N(R')SO_2R'')O-$, $-OP(=W)(-N(R')C(O)R'')O-$, $-OP(=W)(-N(R'')_2)O-$, $-OP(=W)(-N(R')P(O)(R'')_2)O-$, $-P(=W)(-N=C(R'')_2)O-$, $-P(=W)(-N(R')SO_2R'')O-$, $-P(=W)(-N(R')C(O)R'')O-$, $-P(=W)(-N(R'')_2)O-$, or $-P(=W)(-N(R')P(O)(R'')_2)O-$, or a salt form thereof, wherein:

W is O or S;

each R'' is independently R', $-OR'$, $-P(=W)(R')_2$, or $-N(R')_2$;

each R' is independently $-R$, $-C(O)R$, $-C(O)N(R)_2$, $-C(O)OR$, or $-S(O)_2R$;

each R is independently $-H$, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

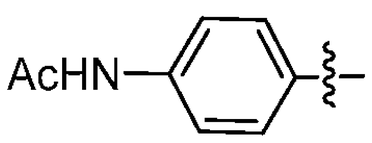
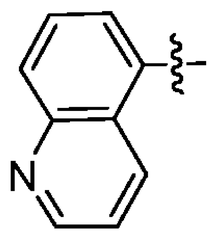
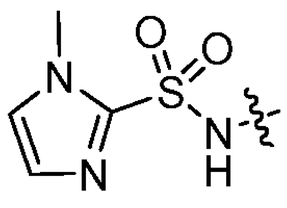
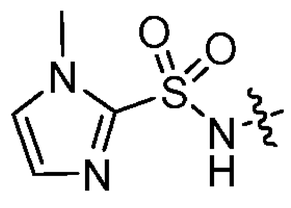
[00836] In some embodiments, W is O. In some embodiments, an internucleotidic linkage has the structure of $-P(=O)(-N=C(R'')_2)-$, $-P(=O)(-N(R')SO_2R'')-$, $-P(=O)(-N(R')C(O)R'')-$, $-P(=O)(-N(R'')_2)-$,

−P(=O)(−N(R’)P(O)(R”)$_2$)−, −OP(=O)(−N=C(R”)$_2$)O−, −OP(=O)(−N(R’)SO$_2$R”)O−, −OP(=O)(−N(R’)C(O)R”)O−, −OP(=O)(−N(R”)$_2$)O−, −OP(=O)(−N(R’)P(O)(R”)$_2$)O−, −P(=O)(−N=C(R”)$_2$)O−, −P(=O)(−N(R’)SO$_2$R”)O−, −P(=O)(−N(R’)C(O)R”)O−, −P(=O)(−N(R”)$_2$)O−, or −P(=O)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N=C(R”)$_2$)− −P(=O)(−N(R”)$_2$)−, −OP(=O)(−N=C(R”)$_2$)−O−, −OP(=O)(−N(R”)$_2$)−O−, −P(=O)(−N=C(R”)$_2$)−O− or −P(=O)(−N(R”)$_2$)−O− or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N=C(R”)$_2$)−O− or −OP(=O)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N=C(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)SO$_2$R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)C(O)R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, a internucleotidic linkage is n001.

[00837] In some embodiments, W is S. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N=C(R”)$_2$)−, −P(=S)(−N(R’)SO$_2$R”)−, −P(=S)(−N(R’)C(O)R”)−, −P(=S)(−N(R”)$_2$)−, −P(=S)(−N(R’)P(O)(R”)$_2$)−, −OP(=S)(−N=C(R”)$_2$)O−, −OP(=S)(−N(R’)SO$_2$R”)O−, −OP(=S)(−N(R’)C(O)R”)O−, −OP(=S)(−N(R”)$_2$)O−, −OP(=S)(−N(R’)P(O)(R”)$_2$)O−, −P(=S)(−N=C(R”)$_2$)O−, −P(=S)(−N(R’)SO$_2$R”)O−, −P(=S)(−N(R’)C(O)R”)O−, −P(=S)(−N(R”)$_2$)O−, or −P(=S)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N=C(R”)$_2$)− −P(=S)(−N(R”)$_2$)−, −OP(=S)(−N=C(R”)$_2$)−O−, −OP(=S)(−N(R”)$_2$)−O−, −P(=S)(−N=C(R”)$_2$)−O− or −P(=S)(−N(R”)$_2$)−O− or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N=C(R”)$_2$)−O− or −OP(=S)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N=C(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R’)SO$_2$R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R’)C(O)R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, a internucleotidic linkage is *n001.

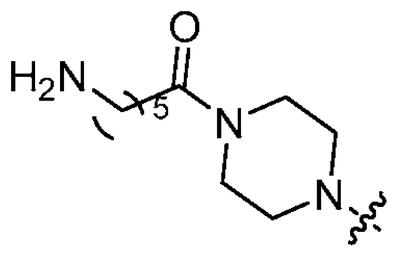
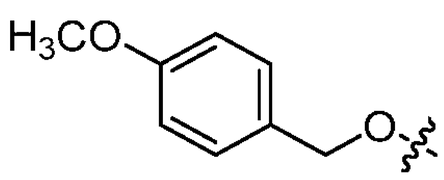
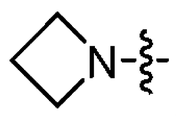
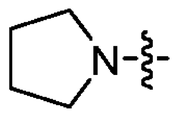
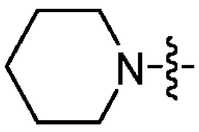
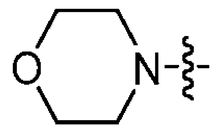
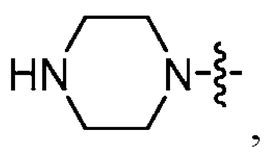
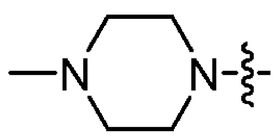
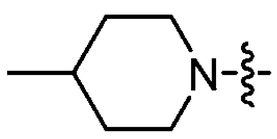
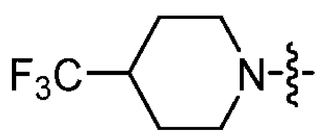
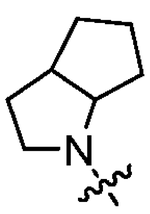
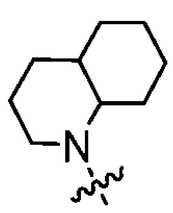
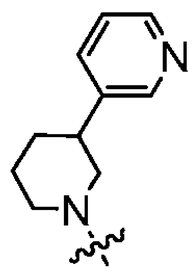
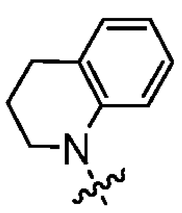
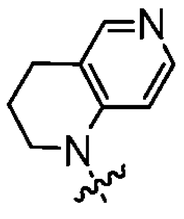
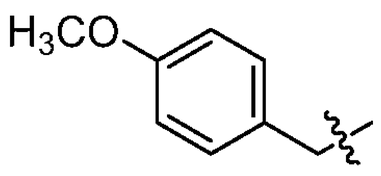
[00838] In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R’)SO$_2$R”)−, wherein R” is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R’)SO$_2$R”)−, wherein R” is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R’)SO$_2$R”)O−, wherein R” is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R’)SO$_2$R”)O−, wherein R” is as described herein. In

some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, R', e.g., of −N(R')−, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in −SO_2R", is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHSO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHSO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, −X−R^L is −N(R')SO_2R^L, wherein each of R' and R^L is independently as described herein. In some embodiments, R^L is R". In some embodiments, R^L is R'. In some embodiments, −X−R^L is −N(R')SO_2R", wherein R' is as described herein. In some embodiments, −X−R^L is −N(R')SO_2R', wherein R' is as described herein. In some embodiments, −X−R^L is −NHSO_2R', wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is optionally substituted heteroaryl. In some embodiments, R", e.g., in −SO_2R", is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is optionally substituted methyl. In some embodiments, −X−R^L is −NHSO_2CH_3. In some embodiments, R is −CF_3. In some embodiments, R is methyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is −CH_2CHF_2. In some embodiments, R is −$CH_2CH_2OCH_3$. In some embodiments, R is optionally substituted propyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is n-butyl. In some embodiments, R is −$(CH_2)_6NH_2$. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-20} alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is p-methylphenyl.

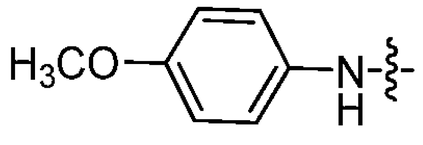
In some embodiments, R is 4-dimethylaminophenyl. In some embodiments, R is 3-pyridinyl. In some embodiments, R is  . In some embodiments, R is  . In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some embodiments, R is isopropyl. In some embodiments, R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, R", e.g., in $-SO_2R$", is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R" is $-OCH_3$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2R)O-$, wherein R is as described herein. In some embodiments, R is optionally substituted linear alkyl as described herein. In some embodiments, R is linear alkyl as described herein. In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH_3)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH_2CH_3)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH_2CH_2OCH_3)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH_2Ph)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH_2CHF_2)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2(4\text{-methylphenyl}))O-$. In some embodiments, $-X-R^L$ is  . In some embodiments, a linkage is $-OP(=O)(-X-R^L)O-$, wherein $-X-R^L$ is  . In some embodiments, a linkage is $-OP(=O)(-NHSO_2CH(CH_3)_2)O-$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2N(CH_3)_2)O-$. In some embodiments, a linkage is n002. In some embodiments, a linkage is n006. In some embodiments, a linkage is n020. In some embodiments, such internucleotidic linkages may be utilized in place of linkages like n001.

[00839] In some embodiments, an internucleotidic linkage has the structure of $-P(=O)(-N(R')C(O)R")-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=S)(-N(R')C(O)R")-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=O)(-N(R')C(O)R")O-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=S)(-N(R')C(O)R")O-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of $-OP(=O)(-N(R')C(O)R")O-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of $-OP(=S)(-N(R')C(O)R")O-$, wherein R" is as described herein. In some embodiments, R', e.g., of $-N(R')-$, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in $-C(O)R"$, is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=O)(-NHC(O)R")-$, wherein R" is as described herein. In some embodiments, an internucleotidic linkage

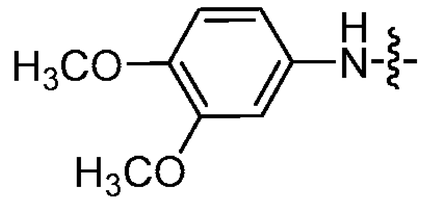
has the structure of −P(=S)(−NHC(O)R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, $-X-R^L$ is $-N(R')COR^L$, wherein R^L is as described herein. In some embodiments, $-X-R^L$ is −N(R')COR", wherein R" is as described herein. In some embodiments, $-X-R^L$ is −N(R')COR', wherein R' is as described herein. In some embodiments, $-X-R^L$ is −NHCOR', wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is optionally substituted heteroaryl. In some embodiments, R", e.g., in −C(O)R", is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is methyl. In some embodiments, $-X-R^L$ is $-NHC(O)CH_3$. In some embodiments, R is optionally substituted methyl. In some embodiments, R is $-CF_3$. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is $-CH_2CHF_2$. In some embodiments, R is $-CH_2CH_2OCH_3$. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) aliphatic. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) alkyl. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-20} alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is p-methylphenyl. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some

embodiments, R^L is $-(CH_2)_5NH_2$. In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, $-X-R^L$ is $-N(R')CON(R^L)_2$, wherein each of R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-NHCON(R^L)_2$, wherein R^L is as described herein. In some embodiments, two R' or two R^L are taken together with the nitrogen atom to which they are attached to form a ring as described herein, e.g., optionally substituted  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R", e.g., in $-C(O)R"$, is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, is optionally substituted C_{1-6} aliphatic. In some embodiments, is optionally substituted C_{1-6} alkyl. In some embodiments, R" is $-OCH_3$. In some embodiments, $-X-R^L$ is $-N(R')C(O)OR^L$, wherein each of R' and R^L is independently as described herein. In some embodiments, R is  . In some embodiments, $-X-R^L$ is $-NHC(O)OCH_3$. In some embodiments, $-X-R^L$ is $-NHC(O)N(CH_3)_2$. In some embodiments, a linkage is $-OP(O)(NHC(O)CH_3)O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)OCH_3)O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)(p\text{-methylphenyl}))O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)N(CH_3)_2)O-$. In some embodiments, $-X-R^L$ is $-N(R')R^L$, wherein each of R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-N(R')R^L$, wherein each of R' and R^L is independently not hydrogen. In some embodiments, $-X-R^L$ is $-NHR^L$, wherein R^L is as described herein. In some embodiments, R^L is not hydrogen. In some embodiments, R^L is optionally substituted aryl or heteroaryl. In some embodiments, R^L is optionally substituted aryl. In some embodiments, R^L is optionally substituted phenyl. In some embodiments, $-X-R^L$ is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, $-X-R^L$ is $-NHR'$, wherein R' is as described herein. In some embodiments, $-X-R^L$ is $-NHR$, wherein R is as described herein. In some embodiments, $-X-R^L$ is R^L, wherein R^L is as described herein. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, R^L is $-NHR'$, wherein R' is as

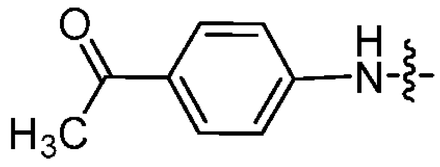
described herein. In some embodiments, R^L is −NHR, wherein R is as described herein. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, none of R' in $-N(R')_2$ is hydrogen. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently C_{1-6} aliphatic. In some embodiments, R^L is −L−R', wherein each of L and R' is independently as described herein. In some embodiments, R^L is −L−R, wherein each of L and R is independently as described herein. In some embodiments, R^L is −N(R')−Cy−N(R')−R'. In some embodiments, R^L is −N(R')−Cy−C(O)−R'. In some embodiments, R^L is −N(R')−Cy−O−R'. In some embodiments, R^L is $-N(R')-Cy-SO_2-R'$. In some embodiments, R^L is $-N(R')-Cy-SO_2-N(R')_2$. In some embodiments, R^L is $-N(R')-Cy-C(O)-N(R')_2$. In some embodiments, R^L is $-N(R')-Cy-OP(O)(R'')_2$. In some embodiments, −Cy− is an optionally substituted bivalent aryl group. In some embodiments, −Cy− is optionally substituted phenylene. In some embodiments, −Cy− is optionally substituted 1,4-phenylene. In some embodiments, −Cy− is 1,4-phenylene. In some embodiments, R^L is $-N(CH_3)_2$. In some embodiments, R^L is $-N(i\text{-}Pr)_2$. In some embodiments, R^L is



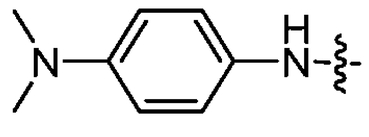
. In some embodiments, R^L is



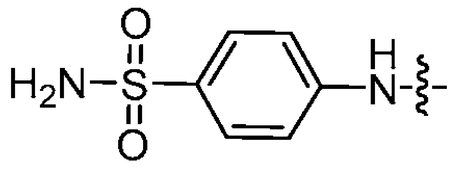
. In some embodiments, R^L is



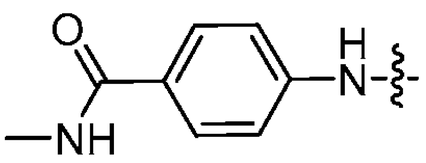
. In some embodiments, R^L is



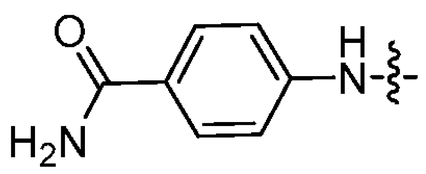
. In some embodiments, R^L is



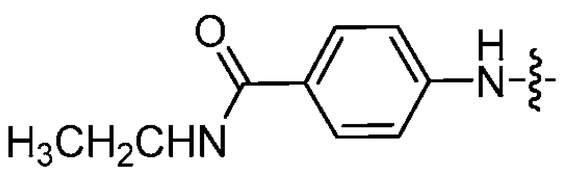
. In some embodiments, R^L is



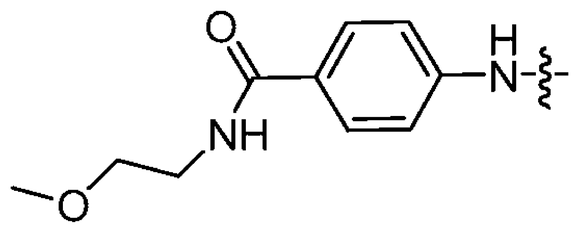
. In some embodiments, R^L is



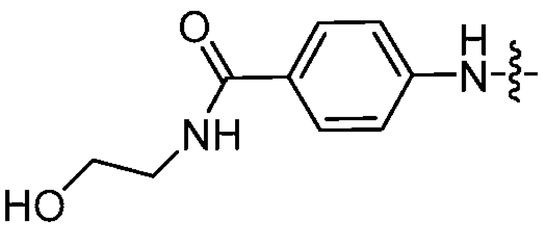
. In some embodiments, R^L is



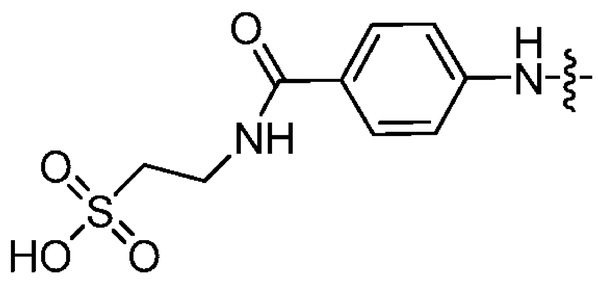
. In some embodiments, R^L is



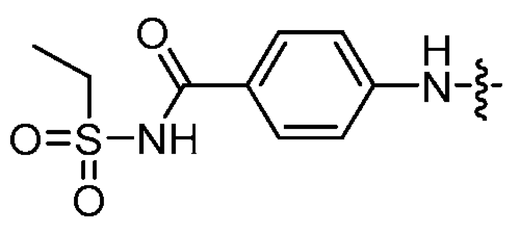
. In some embodiments, R^L is



. In some embodiments, R^L is



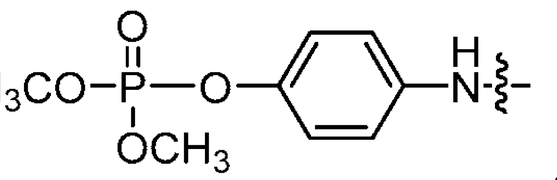
. In some embodiments, R^L is



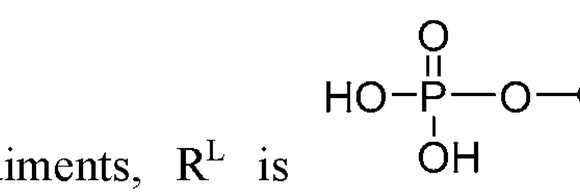
.

In some embodiments, R^L is

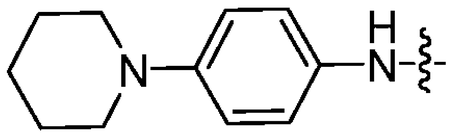
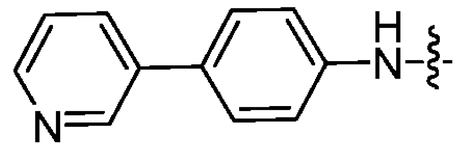
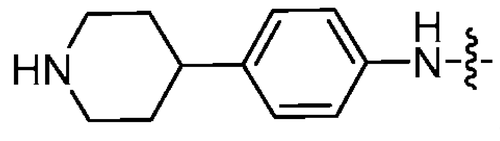
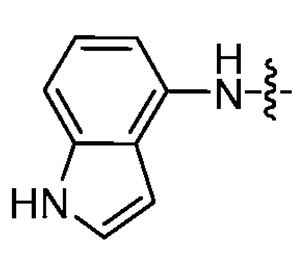
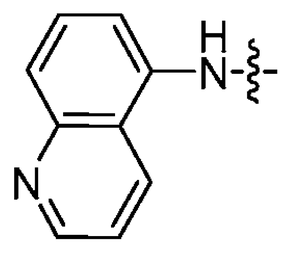
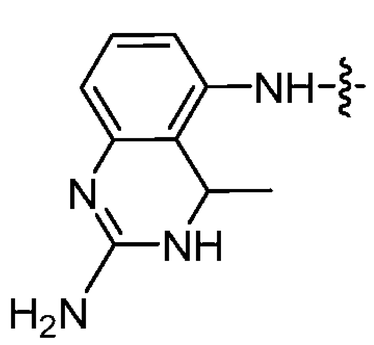
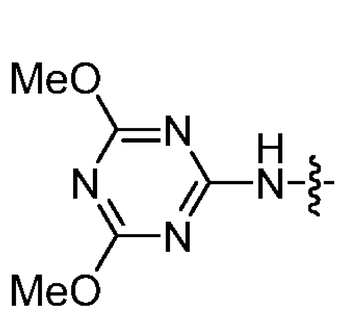
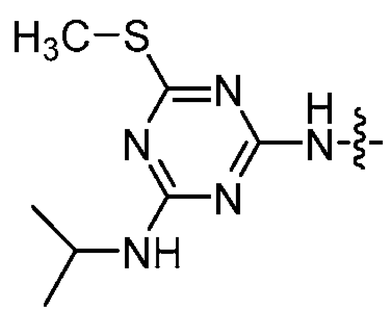
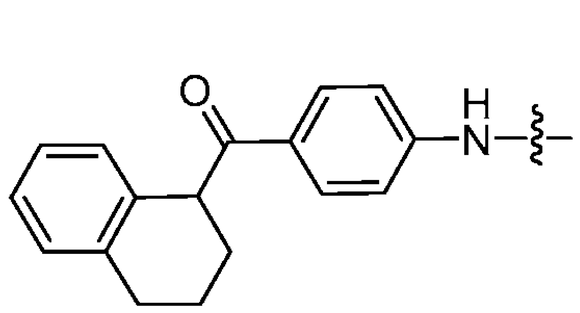
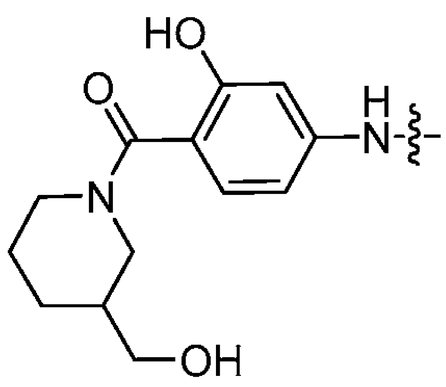
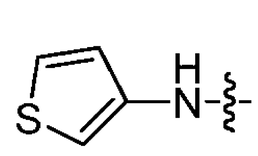
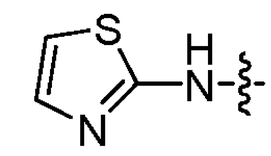
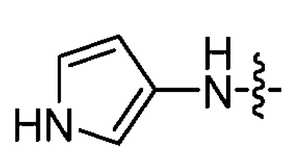
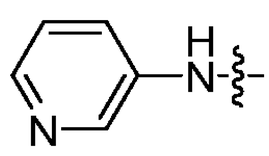
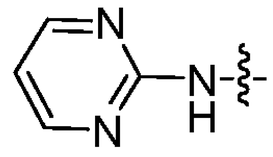
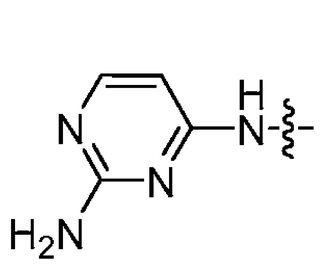
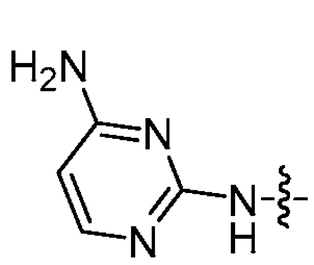
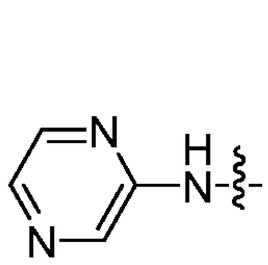
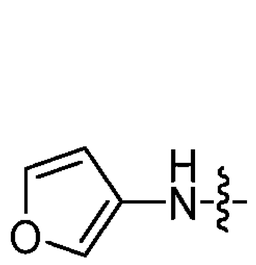
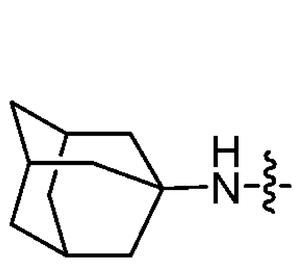
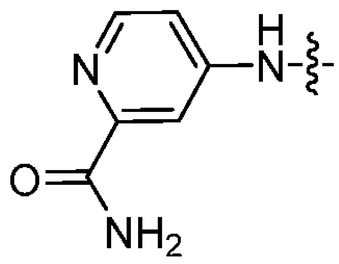
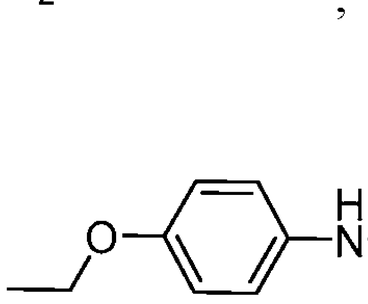
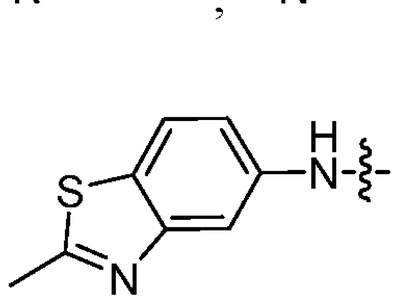
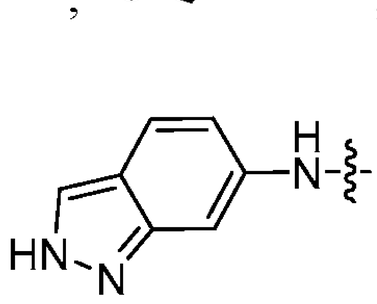
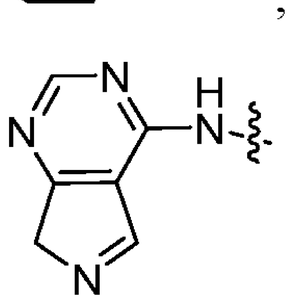
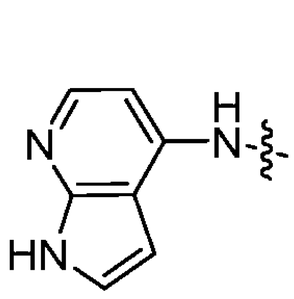
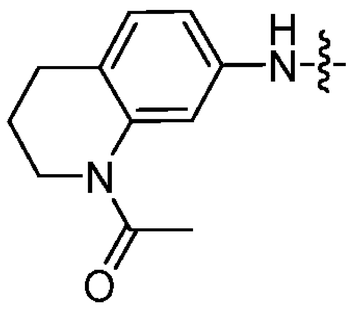
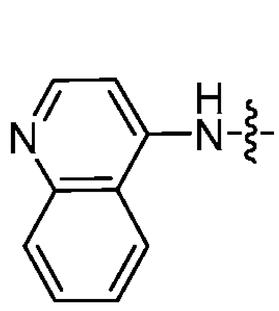
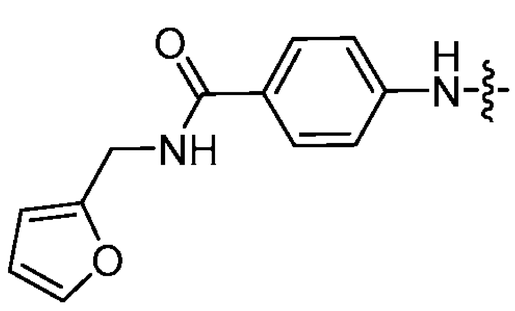
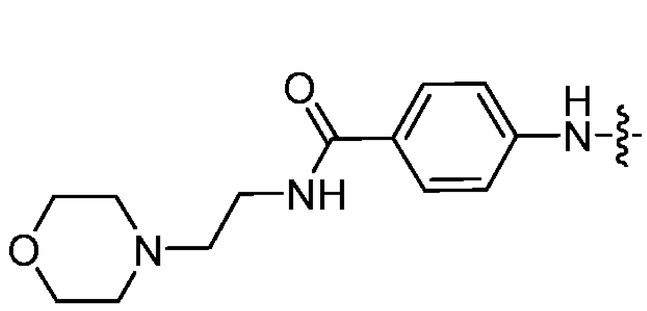
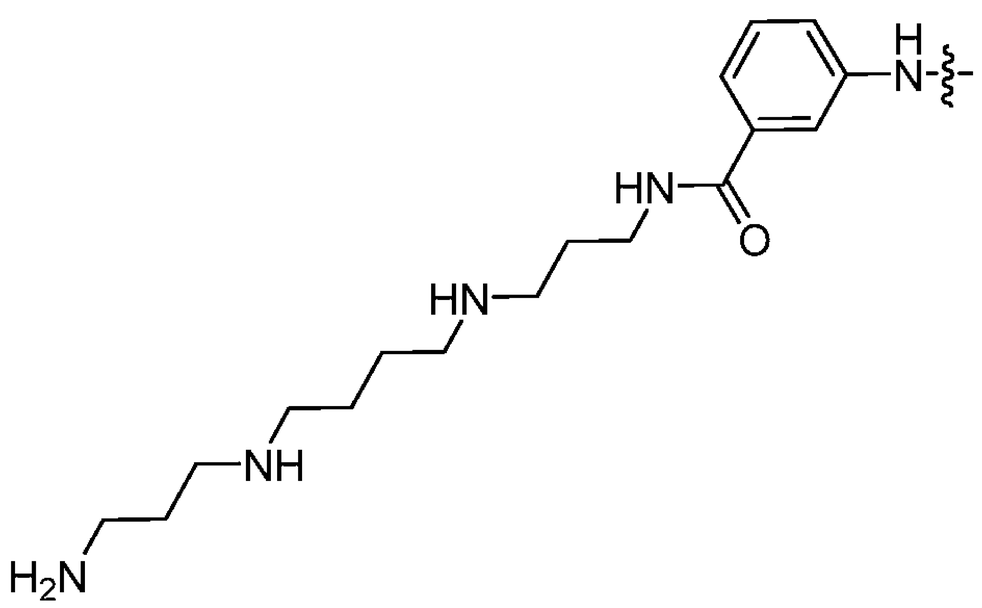
. In some embodiments, R^L is

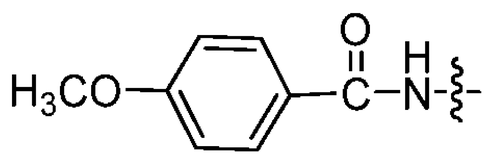
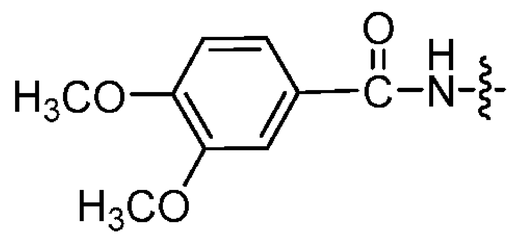
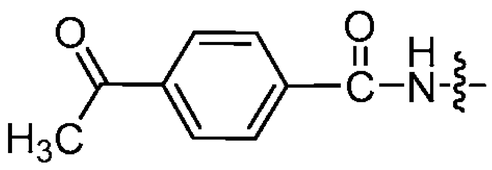
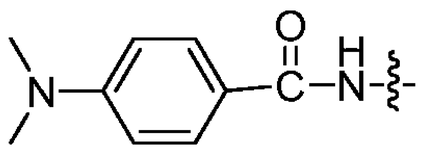
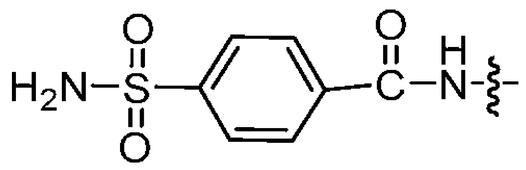
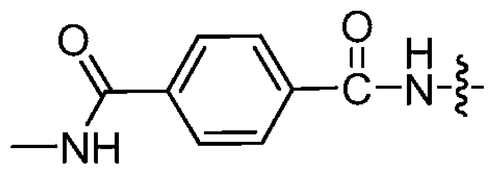
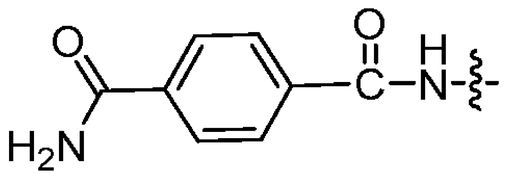
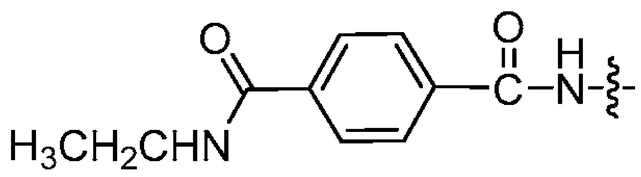
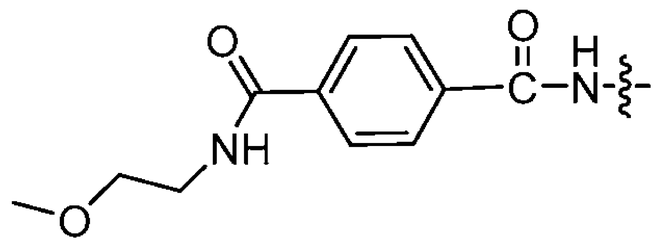
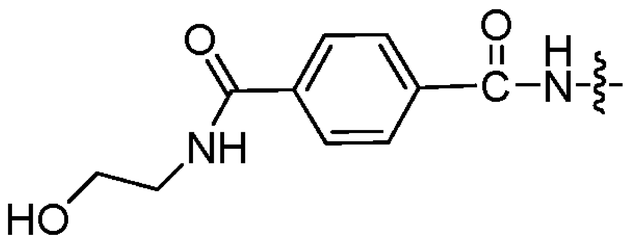
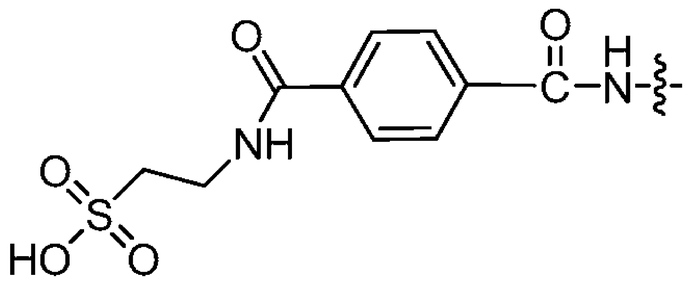
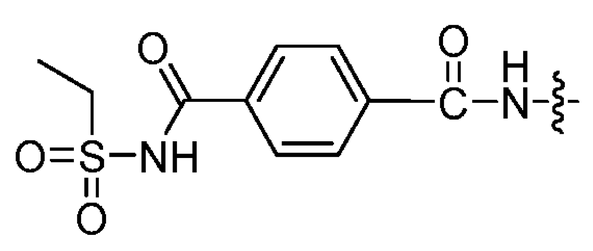
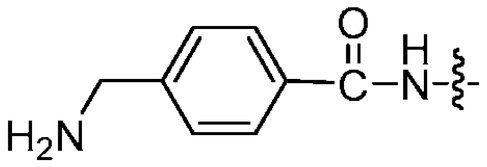
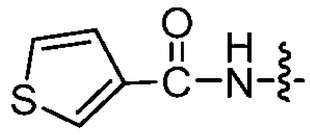
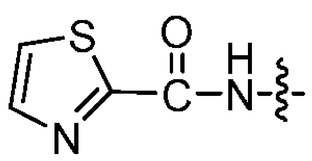
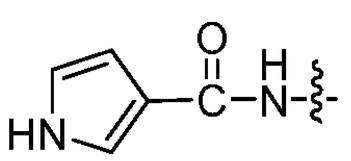
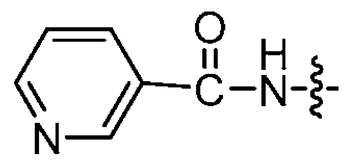
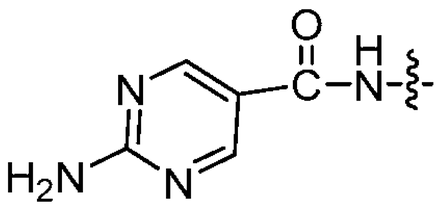
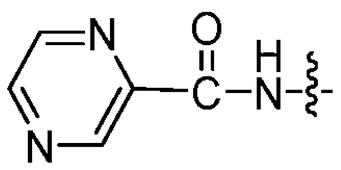
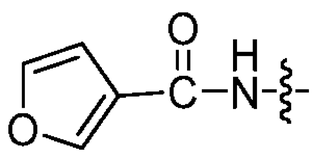
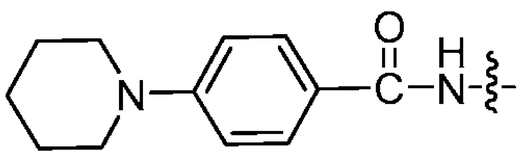
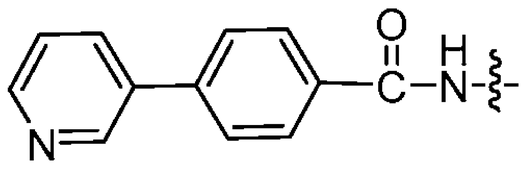
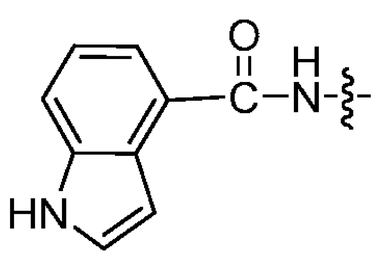
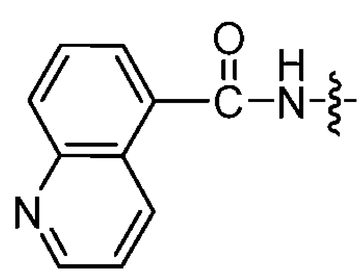
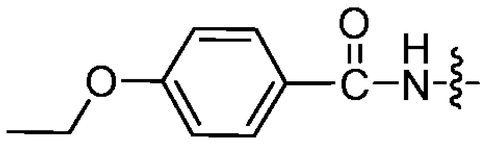
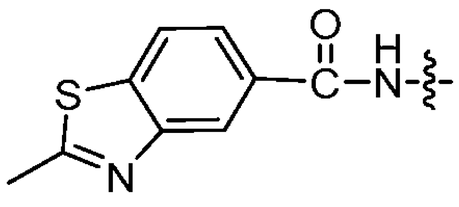
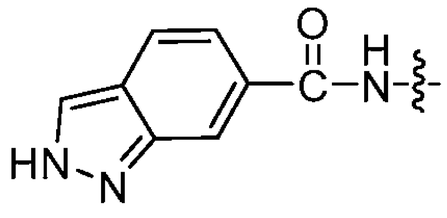


. In some embodiments, R^L is



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embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, $-X-R^L$ is $-N(R')-C(O)-Cy-R^L$. In some embodiments, $-X-R^L$ is R^L. In some embodiments, R^L is $-N(R')-C(O)-Cy-O-R'$. In some

embodiments, R^L is −N(R')−C(O)−Cy−R'. In some embodiments, R^L is −N(R')−C(O)−Cy−C(O)−R'. In some embodiments, R^L is −N(R')−C(O)−Cy−N(R')$_2$. In some embodiments, R^L is −N(R')−C(O)−Cy−SO_2−N(R')$_2$. In some embodiments, R^L is −N(R')−C(O)−Cy−C(O)−N(R')$_2$. In some embodiments, R^L is −N(R')−C(O)−Cy−C(O)−N(R')−SO_2−R'. In some embodiments, R' is R as described herein. In some embodiments, R^L is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[00840] As described herein, in some embodiments, one or more methylene units of L, or a variable which comprises or is L, are independently replaced with −O−, −N(R')−, −C(O)−, −C(O)N(R')−, −SO_2−, −SO_2N(R')−, or −Cy−. In some embodiments, a methylene unit is replaced with −Cy−. In some embodiments, −Cy− is an optionally substituted bivalent aryl group. In some embodiments, −Cy− is optionally substituted phenylene. In some embodiments, −Cy− is optionally substituted 1,4-phenylene. In some embodiments, −Cy− is an optionally substituted bivalent 5-20 (e.g. 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20)

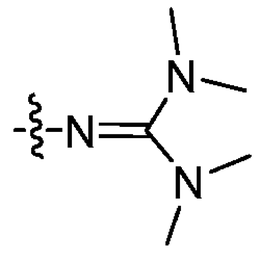
membered heteroaryl group having 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) heteroatoms. In some embodiments, −Cy− is monocyclic. In some embodiments, −Cy− is bicyclic. In some embodiments, −Cy− is polycyclic. In some embodiments, each monocyclic unit in −Cy− is independently 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered, and is independently saturated, partially saturated, or aromatic. In some embodiments, −Cy− is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) membered monocyclic, bicyclic or polycyclic aliphatic group. In some embodiments, −Cy− is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) membered monocyclic, bicyclic or polycyclic heteroaliphatic group having 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) heteroatoms.

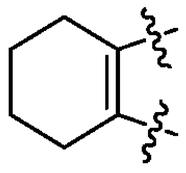
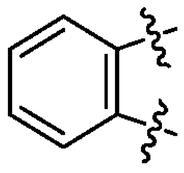
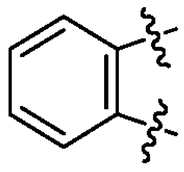
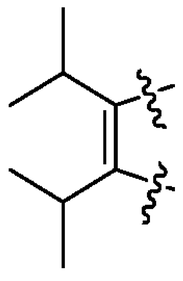
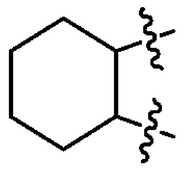
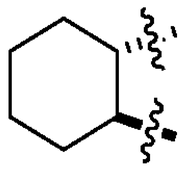
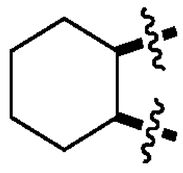
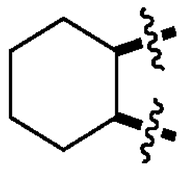
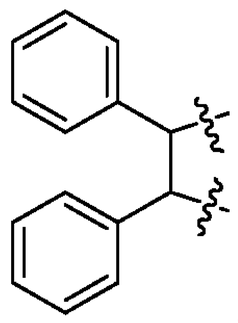
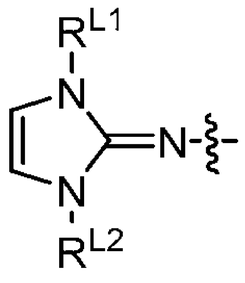
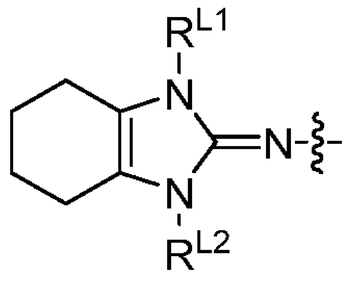
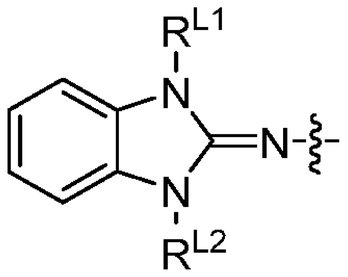
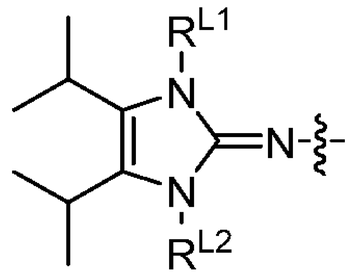
[00841] In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')P(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')P(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, R', e.g., of −N(R')−, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in −P(O)(R")$_2$, is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHP(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHP(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an occurrence of R", e.g., in −P(O)(R")$_2$, is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is $-CF_3$. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is $-CH_2CHF_2$. In some embodiments, R is $-CH_2CH_2OCH_3$. In some

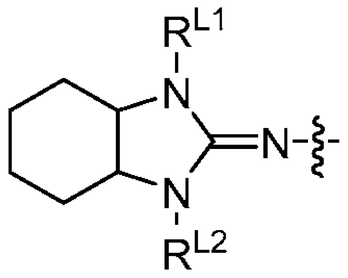
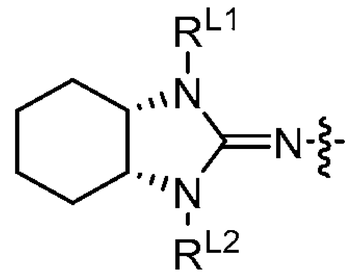
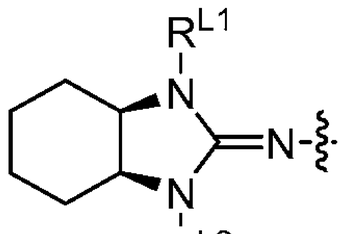
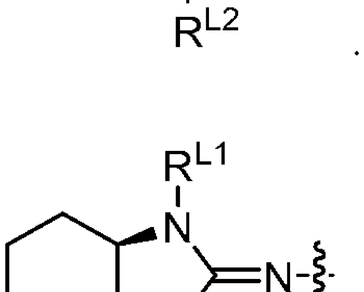
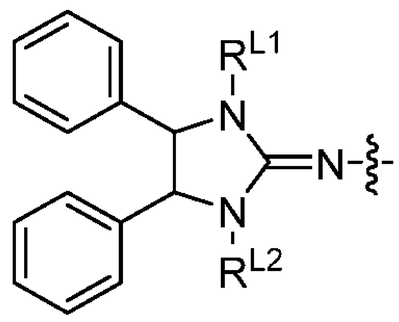
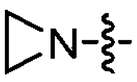
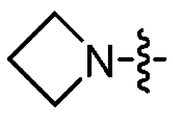
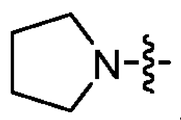
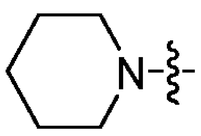
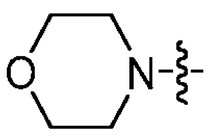
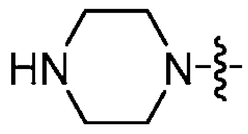
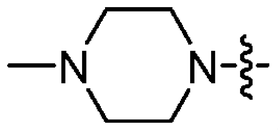
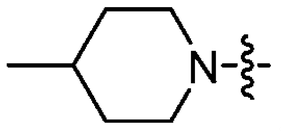
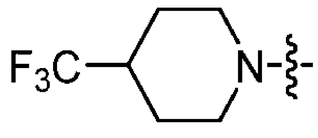
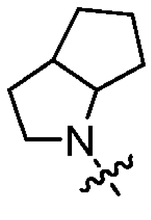
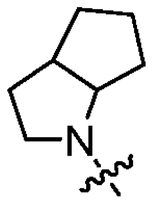
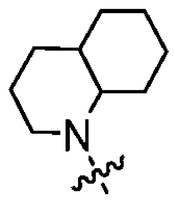
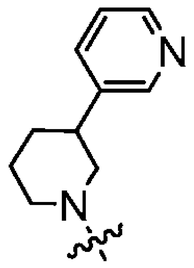
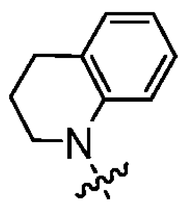
embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) aliphatic. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) alkyl. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-20} alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is isopropyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, each R" is independently R as described herein, for example, in some embodiments, each R" is methyl. In some embodiments, R" is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is p-methylphenyl. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some embodiments, an occurrence of R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, an occurrence of R", e.g., in $-P(O)(R")_2$, is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, is optionally substituted C_{1-6} aliphatic. In some embodiments, is optionally substituted C_{1-6} alkyl. In some embodiments, R" is $-OCH_3$. In some embodiments, each R" is $-OR'$ as described herein. In some embodiments, each R" is $-OCH_3$. In some embodiments, each R" is $-OH$. In some embodiments, a linkage is $-OP(O)(NHP(O)(OH)_2)O-$. In some embodiments, a linkage is $-OP(O)(NHP(O)(OCH_3)_2)O-$. In some embodiments, a linkage is $-OP(O)(NHP(O)(CH_3)_2)O-$.

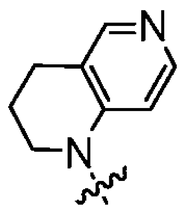
[00842] In some embodiments, $-N(R")_2$ is $-N(R')_2$. In some embodiments, $-N(R")_2$ is $-NHR$. In some embodiments, $-N(R")_2$ is $-NHC(O)R$. In some embodiments, $-N(R")_2$ is $-NHC(O)OR$. In some embodiments, $-N(R")_2$ is $-NHS(O)_2R$.

[00843] In some embodiments, an internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, an internucleotidic linkage comprises $-X-R^L$ as described herein. In some embodiments, $-X-R^L$ is $-N=C(-L^L-R^L)_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2]_2$. In some embodiments, $-X-R^L$ is $-N=C[NR'R^L]_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2]_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2](CHR^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(CHR^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(CR'R^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2](CHR'R^{L2})$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2](R^L)$. In some embodiments,

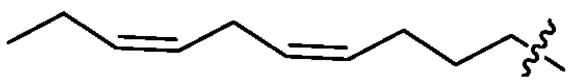
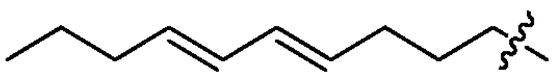
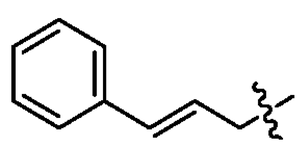
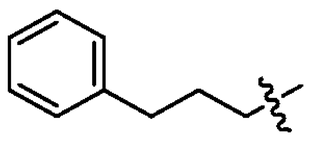
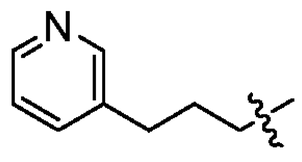
$-X-R^L$ is $-N=C(NR'R^L)(R^L)$. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(R')$. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2](R')$. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(NR'R^{L2})$, wherein each R^{L1} and R^{L2} is independently R^L, and each R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(NR'R^{L2})$, wherein variable is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(CHR'R^{L2})$, wherein variable is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(R')$, wherein variable is independently as described herein. In some embodiments, each R' is independently R. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl. In some embodiments, $-X-R^L$ is  . In some embodiments, two groups selected from R', R^L, R^{L1}, R^{L2}, etc. (in some embodiments, on the same atom (e.g., $-N(R')_2$, or $-NR'R^L$, or $-N(R^L)^2$, wherein R' and R^L can independently be R as described herein), etc.), or on different atoms (e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$ or $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$; can also be two other variables that can be R, e.g., R^L, R^{L1}, R^{L2}, etc.)) are independently R and are taken together with their intervening atoms to form a ring as described herein. In some embodiments, two of R, R', R^L, R^{L1}, or R^{L2} on the same atom, e.g., of $-N(R')_2$, $-N(R^L)_2$, $-NR'R^L$, $-NR'R^{L1}$, $-NR'R^{L2}$, $-CR'R^{L1}R^{L2}$, etc., are taken together to form a ring as described herein. In some embodiments, two R', R^L, R^{L1}, or R^{L2} on two different atoms, e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$, $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, etc. are taken together to form a ring as described herein. In some embodiments, a formed ring is an optionally substituted 3-20 (e.g., 3-15, 3-12, 3-10, 3-9, 3-8, 3-7, 3-6, 4-15, 4-12, 4-10, 4-9, 4-8, 4-7, 4-6, 5-15, 5-12, 5-10, 5-9, 5-8, 5-7, 5-6, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) monocyclic, bicyclic or tricyclic ring having 0-5 additional heteroatoms. In some embodiments, a formed ring is monocyclic as described herein. In some embodiments, a formed ring is an optionally substituted 5-10 membered monocyclic ring. In some embodiments, a formed ring is bicyclic. In some embodiments, a formed ring is polycyclic. In some embodiments, two groups that are or can be R (e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$ or $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$, $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, etc.) are taken together to form an optionally substituted bivalent hydrocarbon chain, e.g., an optionally substituted C_{1-20} aliphatic chain, optionally substituted $-(CH_2)n-$ wherein n is 1-20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20). In some embodiments, a hydrocarbon chain is saturated. In some embodiments, a hydrocarbon chain is partially unsaturated. In some embodiments, a hydrocarbon chain is unsaturated. In some embodiments, two groups that are or can be R (e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$ or $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$, $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, etc.) are taken together to form an optionally substituted bivalent heteroaliphatic chain, e.g., an optionally substituted C_{1-20} heteroaliphatic chain having 1-10 heteroatoms. In some embodiments, a heteroaliphatic chain is saturated. In some embodiments, a heteroaliphatic chain is partially unsaturated. In some embodiments, a heteroaliphatic chain is unsaturated. In

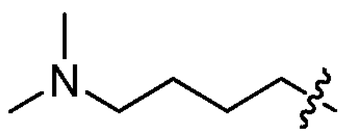
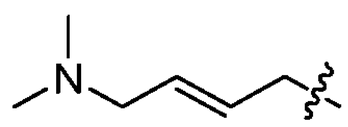
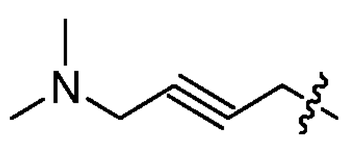
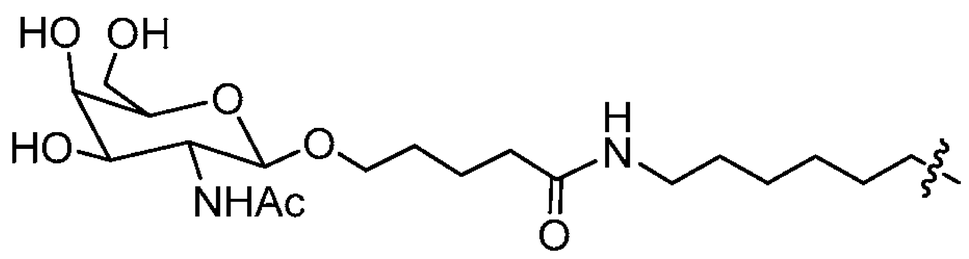
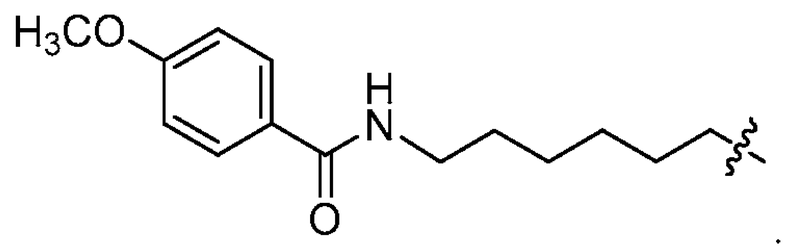
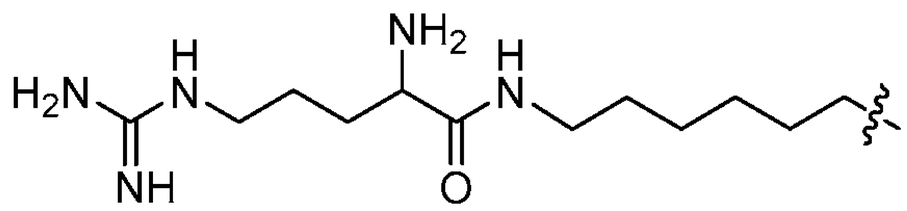
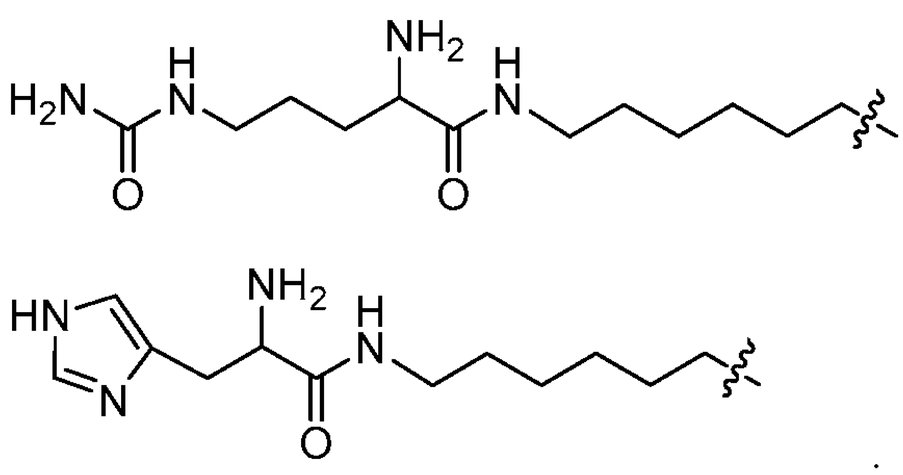
some embodiments, a chain is optionally substituted $-(CH_2)-$. In some embodiments, a chain is optionally substituted $-(CH_2)_2-$. In some embodiments, a chain is optionally substituted $-(CH_2)-$. In some embodiments, a chain is optionally substituted $-(CH_2)_2-$. In some embodiments, a chain is optionally substituted $-(CH_2)_3-$. In some embodiments, a chain is optionally substituted $-(CH_2)_4-$. In some embodiments, a chain is optionally substituted $-(CH_2)_5-$. In some embodiments, a chain is optionally substituted $-(CH_2)_6-$. In some embodiments, a chain is optionally substituted $-CH=CH-$. In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, two of R, R', R^L, R^{L1}, R^{L2}, etc. on different atoms are taken together to form a ring as described herein. For examples, in some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some

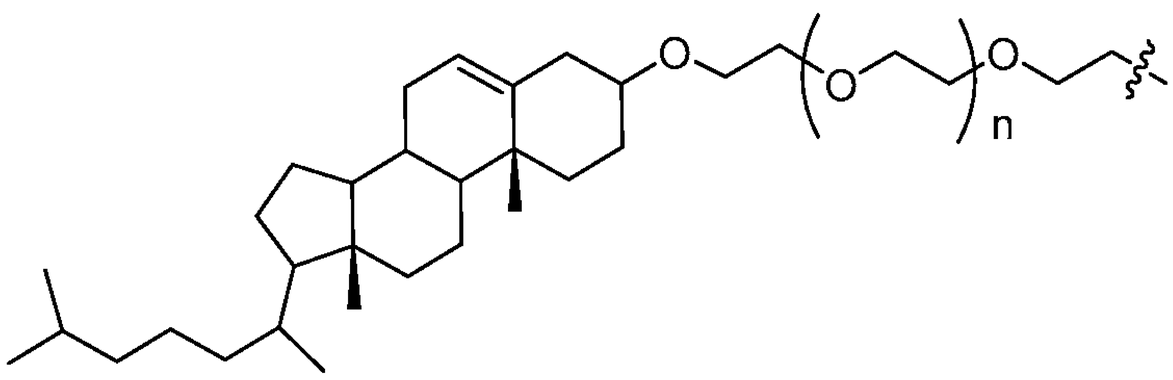
embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is . In some embodiments, $-X-R^L$ is  . In some embodiments, $-N(R')_2$, $-N(R)_2$, $-N(R^L)_2$, $-NR'R^L$, $-NR'R^{L1}$, $-NR'R^{L2}$, $-NR^{L1}R^{L2}$, etc. is a formed ring. In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally

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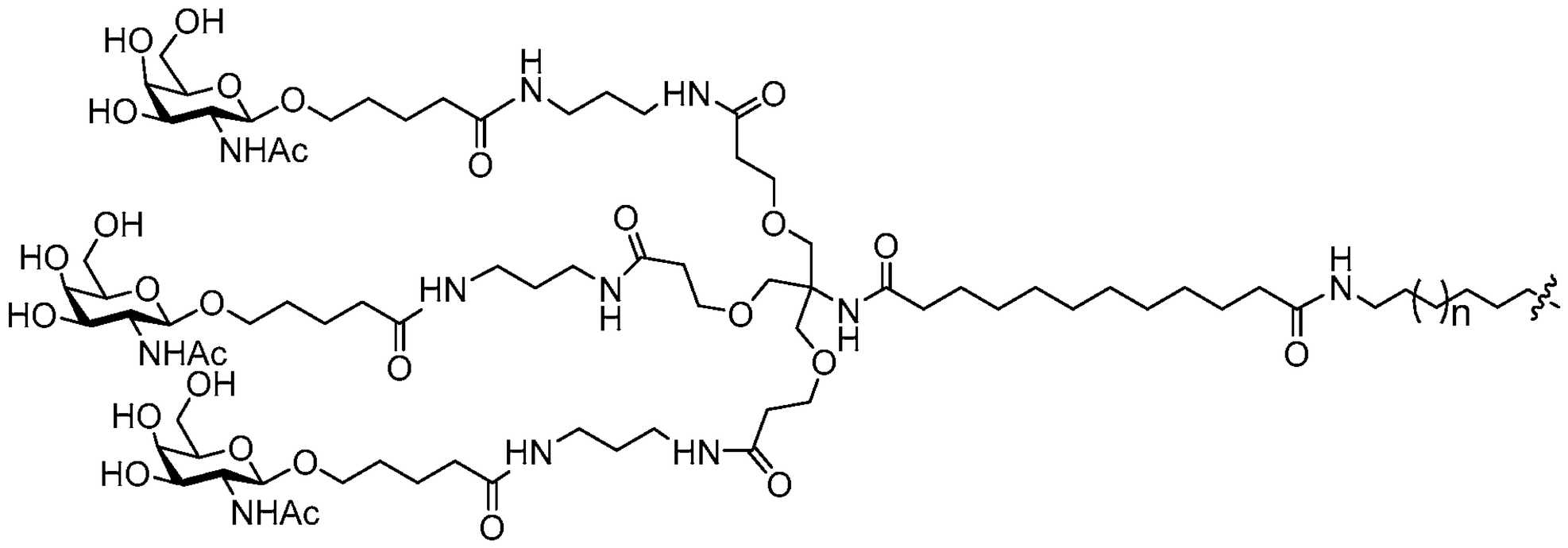
[00844] In some embodiments, R^{L1} and R^{L2} are the same. In some embodiments, R^{L1} and R^{L2} are different. In some embodiments, each of R^{L1} and R^{L2} is independently R^L as described herein, e.g., below.

[00845] In some embodiments, R^L is optionally substituted C_{1-30} aliphatic. In some embodiments, R^L is optionally substituted C_{1-30} alkyl. In some embodiments, R^L is linear. In some embodiments, R^L is optionally substituted linear C_{1-30} alkyl. In some embodiments, R^L is optionally substituted C_{1-6} alkyl. In some embodiments, R^L is methyl. In some embodiments, R^L is ethyl. In some embodiments, R^L is n-propyl. In some embodiments, R^L is isopropyl. In some embodiments, R^L is n-butyl. In some embodiments, R^L is tert-butyl. In some embodiments, R^L is (E)−CH_2−CH=CH−CH_2−CH_3. In some embodiments, R^L is (Z)−CH_2−CH=CH−CH_2−CH_3. In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is $CH_3(CH_2)_2C{\equiv}CC{\equiv}C(CH_2)_3$−. In some embodiments, R^L is $CH_3(CH_2)_5C{\equiv}C$−. In some embodiments, R^L optionally substituted aryl. In some embodiments, R^L is optionally substituted phenyl. In some embodiments, R^L is phenyl substituted with one or more halogen. In some embodiments, R^L is phenyl optionally substituted with halogen, −N(R'), or −N(R')C(O)R'. In some embodiments, R^L is phenyl optionally substituted with −Cl, −Br, −F, −$N(Me)_2$, or −$NHCOCH_3$. In some embodiments, R^L is $-L^L-R'$, wherein L^L is an optionally substituted C_{1-20} saturated, partially unsaturated or unsaturated hydrocarbon chain. In some embodiments, such a hydrocarbon chain is linear. In some embodiments, such a hydrocarbon chain is unsubstituted. In some embodiments, L^L is (E)−CH_2−CH=CH−. In some embodiments, L^L is −CH_2−C≡C−CH_2−. In some embodiments, L^L is −$(CH_2)_3$−. In some embodiments, L^L is −$(CH_2)_4$−. In some embodiments, L^L is −$(CH_2)_n$−, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R' is optionally substituted aryl as described herein. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is phenyl. In some embodiments, R' is optionally substituted heteroaryl as described herein. In some embodiments, R' is 2'-pyridinyl. In some embodiments, R' is 3'-pyridinyl. In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is $-L^L-N(R')_2$, wherein each variable is independently as described herein. In some embodiments, each R' is independently C_{1-6} aliphatic as described herein. In some embodiments, −$N(R')_2$ is −$N(CH_3)_2$. In some embodiments, −$N(R')_2$ is −NH_2. In some embodiments, R^L is −$(CH_2)_n$−$N(R')_2$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In

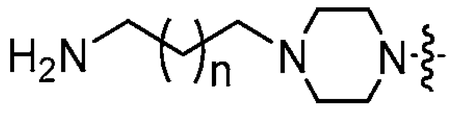
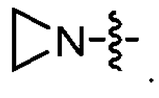
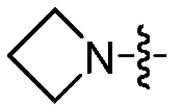
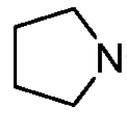
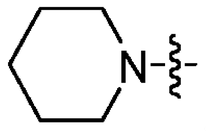
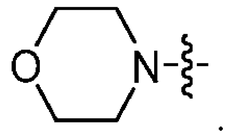
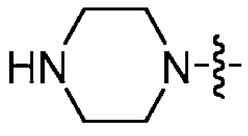
some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-N(R')_2$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is $-(CH_2)_n-NH_2$. In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-NH_2$. In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-R'$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2CH_3$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2OH$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is or comprises a carbohydrate moiety, e.g., GalNAc. In some embodiments, R^L is $-L^L-$GalNAc. In some embodiments, R^L is  . In some embodiments, one or more methylene units of L^L are independently replaced with $-Cy-$ (e.g., optionally substituted 1,4-phenylene, a 3-30 membered bivalent optionally substituted monocyclic, bicyclic, or polycyclic cycloaliphatic ring, etc.), $-O-$, $-N(R')-$ (e.g., $-NH$), $-C(O)-$, $-C(O)N(R')-$ (e.g., $-C(O)NH-$), $-C(NR')-$ (e.g., $-C(NH)-$), $-N(R')C(O)(N(R')-$ (e.g., $-NHC(O)NH-$), $-N(R')C(NR')(N(R')-$ (e.g., $-NHC(NH)NH-$), $-(CH_2CH_2O)_n-$, etc. For example, in some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is . In some embodiments, R^L is

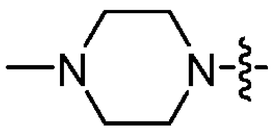
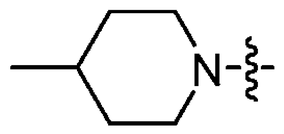
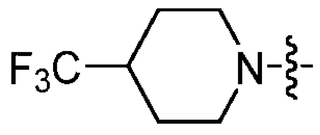
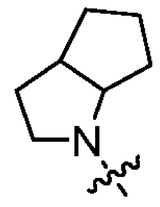
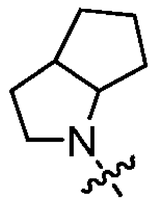
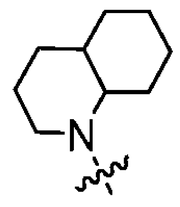
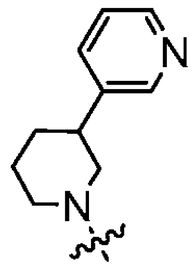
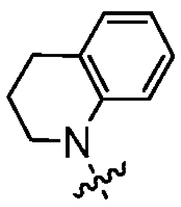
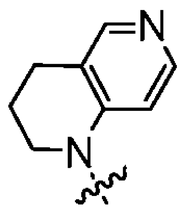


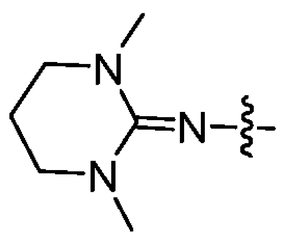
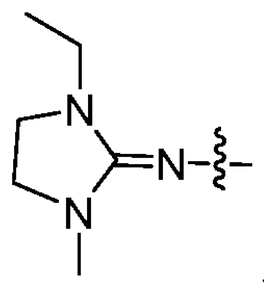
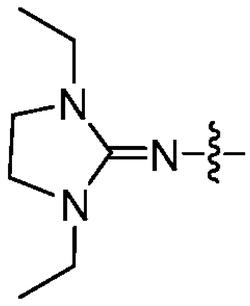
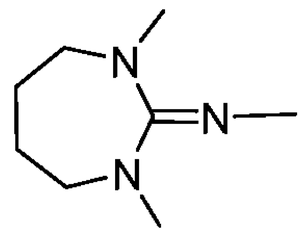
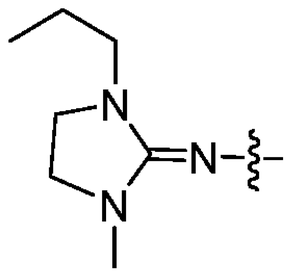
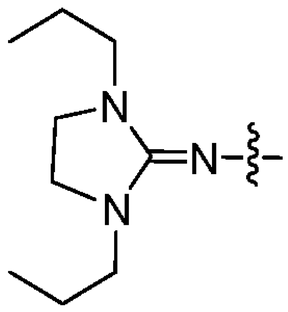
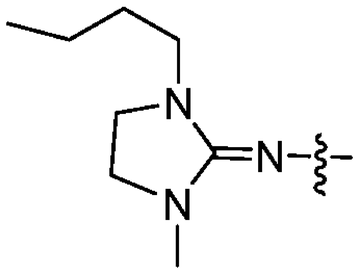
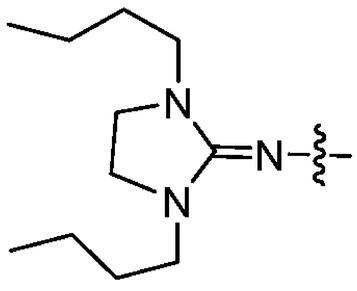
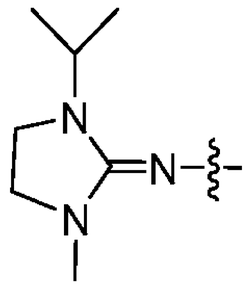
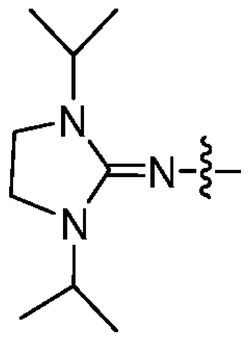
wherein n is 0-20. In some embodiments, R^L is or comprises one or more additional chemical moieties (e.g., carbohydrate moieties, GalNAc moieties, etc.) optionally substituted connected through a linker (which can be bivalent or polyvalent). For example, in some embodiments, R^L is

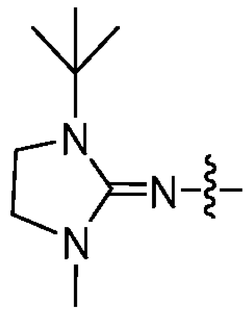
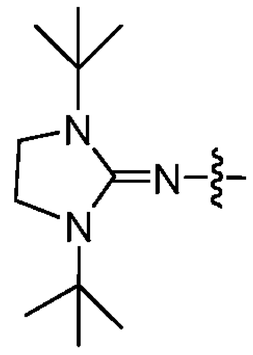
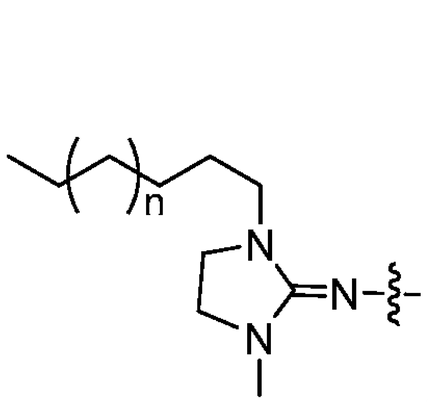
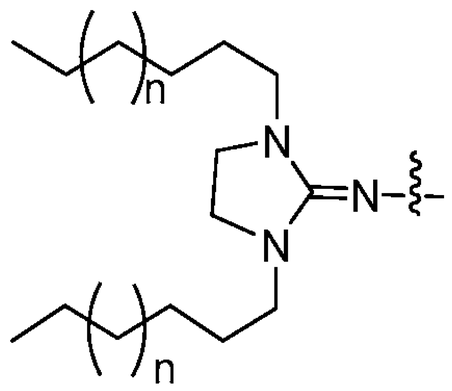


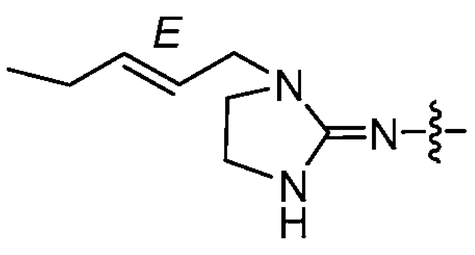
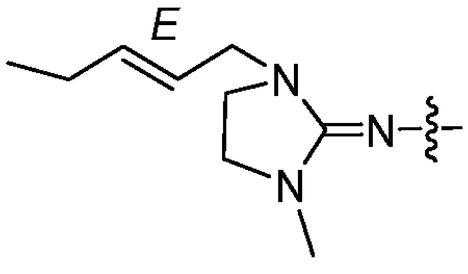
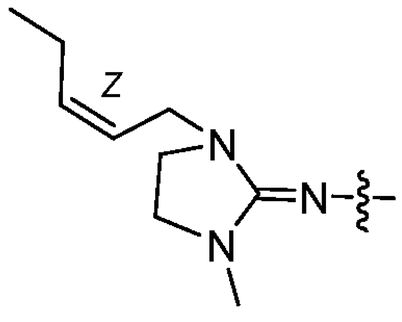
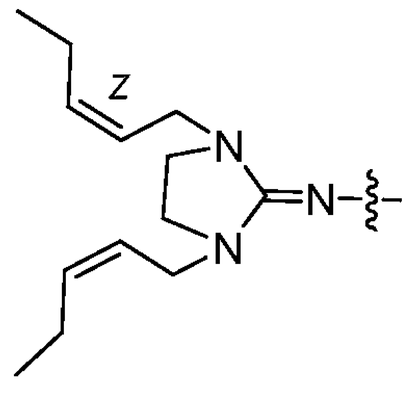
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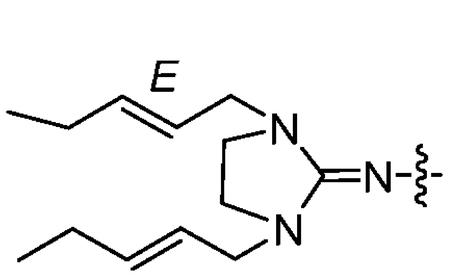
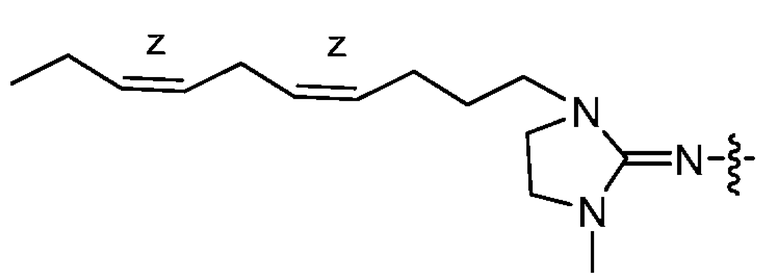
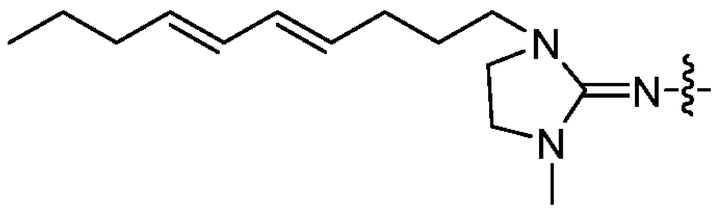
wherein n is 0-20. In some embodiments, R^L is  , wherein n is 0-20. In some embodiments, R^L is R' as described herein. As described herein, many variable can independently be R'. In some embodiments, R' is R as described herein. As described herein, various variables can independently be R. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted cycloaliphatic. In some embodiments, R is optionally substituted cycloalkyl. In some embodiments, R is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted heterocyclyl. In some embodiments, R is optionally substituted C_{1-20} heterocyclyl having 1-5 heteroatoms, e.g., one of which is nitrogen. In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted

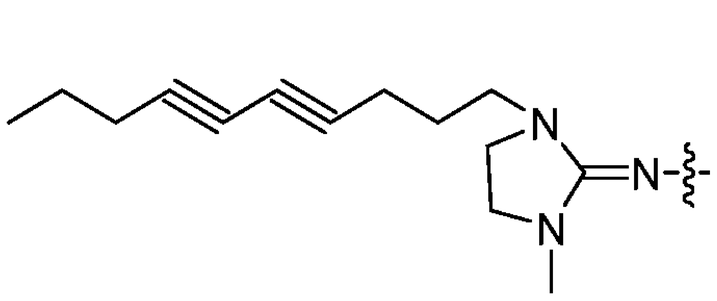
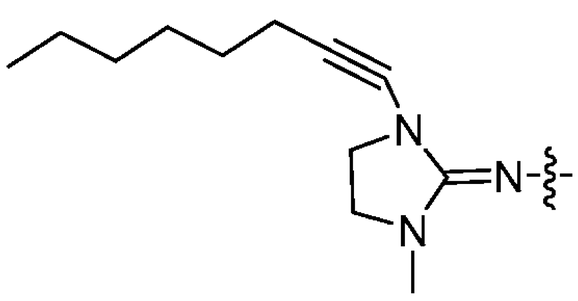
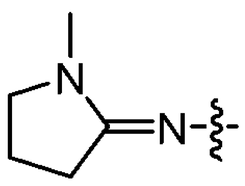
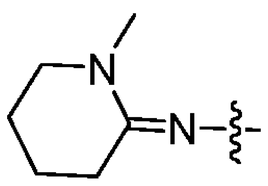
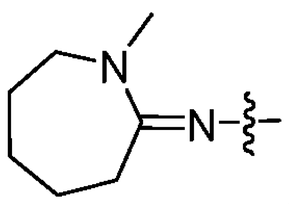

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[00846] In some embodiments, $-X-R^L$ is 
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$-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  , wherein n is 1-20. In some embodiments, $-X-R^L$ is  , wherein n is 1-20. In some embodiments, $-X-R^L$ is selected from:

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 and  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  .

[00847] In some embodiments, R^L is R" as described herein. In some embodiments, R^L is R as described herein.

[00848] In some embodiments, R" or R^L is or comprises an additional chemical moiety. In some embodiments, R" or R^L is or comprises an additional chemical moiety, wherein the additional chemical moiety is or comprises a carbohydrate moiety. In some embodiments, R" or R^L is or comprises a GalNAc. In some embodiments, R^L or R" is replaced with, or is utilized to connect to, an additional chemical moiety.

[00849] In some embodiments, X is –O–. In some embodiments, X is –S–. In some embodiments, X is $-L^L-N(-L^L-R^L)-L^L-$. In some embodiments, X is $-N(-L^L-R^L)-L^L-$. In some embodiments, X is $-L^L-N(-L^L-R^L)-$. In some embodiments, X is $-N(-L^L-R^L)-$. In some embodiments, X is $-L^L-N=C(-L^L-R^L)-L^L-$. In some embodiments, X is $-N=C(-L^L-R^L)-L^L-$. In some embodiments, X is $-L^L-N=C(-L^L-R^L)-$. In some embodiments, X is $-N=C(-L^L-R^L)-$. In some embodiments, X is L^L. In some embodiments, X is a covalent bond.

[00850] In some embodiments, Y is a covalent bond. In some embodiments, Y is −O−. In some embodiments, Y is −N(R')−. In some embodiments, Z is a covalent bond. In some embodiments, Z is −O−. In some embodiments, Z is −N(R')−. In some embodiments, R' is R. In some embodiments, R is −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is propyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

[00851] As described herein, various variables in structures in the present disclosure can be or comprise R. Suitable embodiments for R are described extensively in the present disclosure. As appreciated by those skilled in the art, R embodiments described for a variable that can be R may also be applicable to another variable that can be R. Similarly, embodiments described for a component/moiety (e.g., L) for a variable may also be applicable to other variables that can be or comprise the component/moiety.

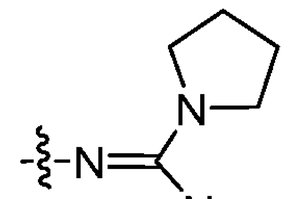
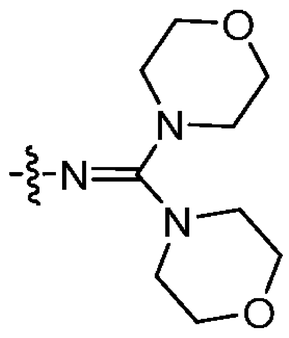
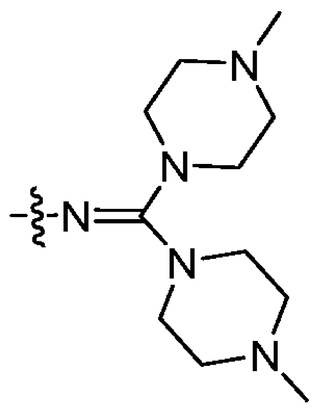
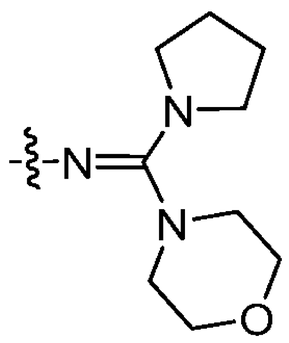
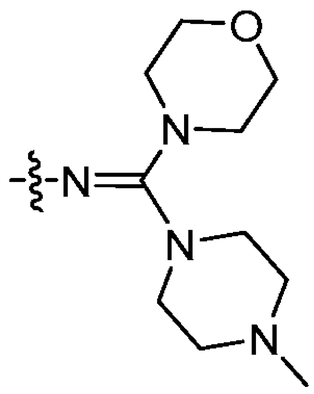
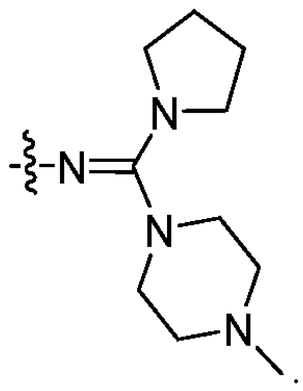
[00852] In some embodiments, R" is R'. In some embodiments, R" is $-N(R')_2$.

[00853] In some embodiments, $-X-R^L$ is −SH. In some embodiments, $-X-R^L$ is −OH.

[00854] In some embodiments, $-X-R^L$ is $-N(R')_2$. In some embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R' is independently methyl.

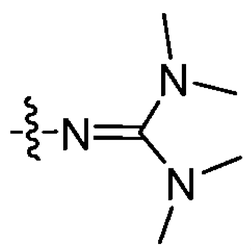
[00855] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of $-OP(=O)(-N=C((N(R')_2)_2-O-$. In some embodiments, a R' group of one $N(R')_2$ is R, a R' group of the other $N(R')_2$ is R, and the two R groups are taken together with their intervening atoms to form an optionally substituted ring, e.g., a 5-membered ring as in n001. In some embodiments, each R' is independently R, wherein each R is independently optionally substituted C_{1-6} aliphatic.

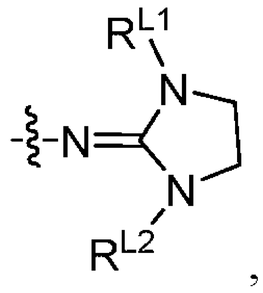
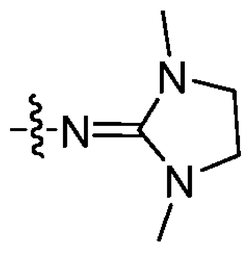
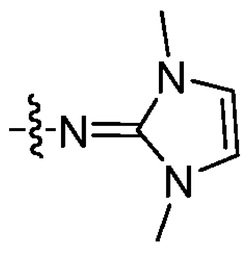
[00856] In some embodiments, $-X-R^L$ is $-N=C(-L^L-R')_2$. In some embodiments, $-X-R^L$ is $-N=C(-L^{L1}-L^{L2}-L^{L3}-R')_2$, wherein each L^{L1}, L^{L2} and L^{L3} is independently L", wherein each L" is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−,

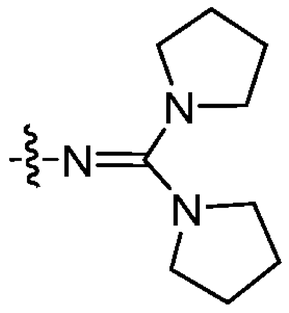
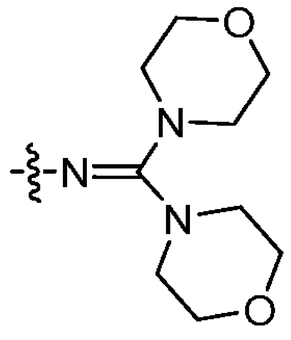
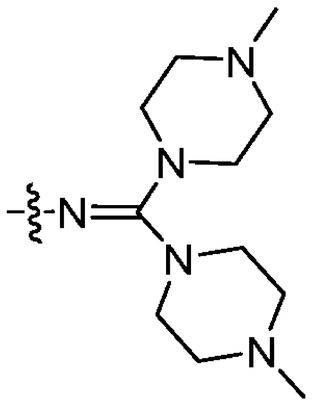
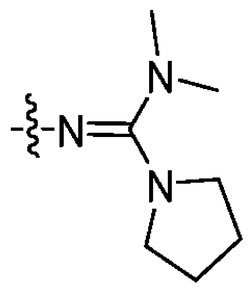
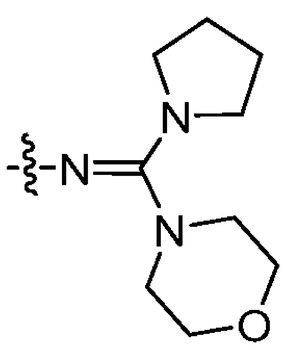
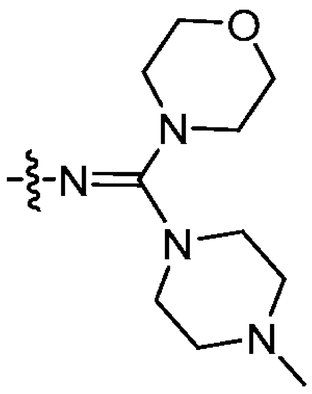
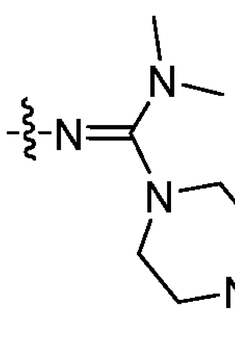
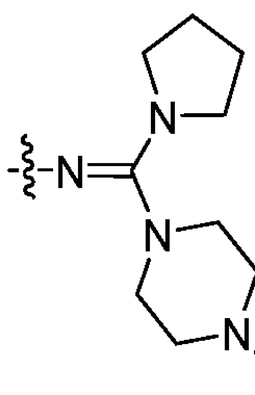
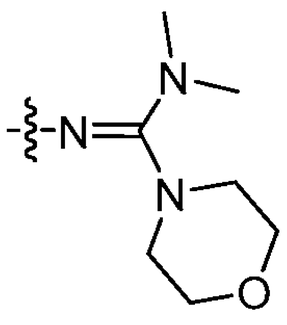
−P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L^{L2} is −Cy−. In some embodiments, L^{L1} is a covalent bond. In some embodiments, L^{L3} is a covalent bond. In some embodiments, −X−R^L is −N=C(−L^{L1}−Cy−L^{L3}−R')$_2$. In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  .

[00857] In some embodiments, as utilized in the present disclosure, L is covalent bond. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, −C(R')$_2$−, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic

group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C$_{1-10}$ aliphatic group and a C$_{1-10}$ heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, –C(O)O–, –P(O)(OR')–, –P(O)(SR')–, –P(O)(R')–, –P(O)(NR')–, –P(S)(OR')–, –P(S)(SR')–, –P(S)(R')–, –P(S)(NR')–, –P(R')–, –P(OR')–, –P(SR')–, –P(NR')–, –P(OR')[B(R')$_3$]–, –OP(O)(OR')O–, –OP(O)(SR')O–, –OP(O)(R')O–, –OP(O)(NR')O–, –OP(OR')O–, –OP(SR')O–, –OP(NR')O–, –OP(R')O–, or –OP(OR')[B(R')$_3$]O–, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, –C(R')$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R')–, –C(O)–, –C(S)–, –C(NR')–, –C(O)N(R')–, –N(R')C(O)N(R')–, –N(R')C(O)O–, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R')–, –C(O)S–, or –C(O)O–.

[00858] In some embodiments, an internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, –X–R^L is –N=C[N(R')$_2$]$_2$. In some embodiments, each R' is independently R. In some embodiments, R is optionally substituted C$_{1-6}$ aliphatic. In some embodiments, R is methyl. In some embodiments, –X–R^L is  . In some embodiments, one R' on a nitrogen atom is taken with a R' on the other nitrogen to form a ring as described herein.

[00859] In some embodiments, –X–R^L is  , wherein R^1 and R^2 are independently R'. In some embodiments, –X–R^L is  . In some embodiments, –X–R^L is  . In some embodiments, two R' on the same nitrogen are taken together to form a ring as described herein. In some embodiments,

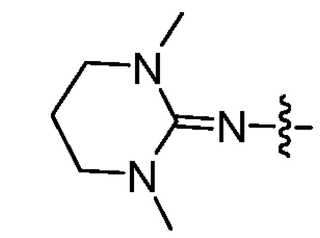
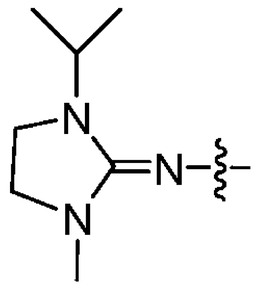
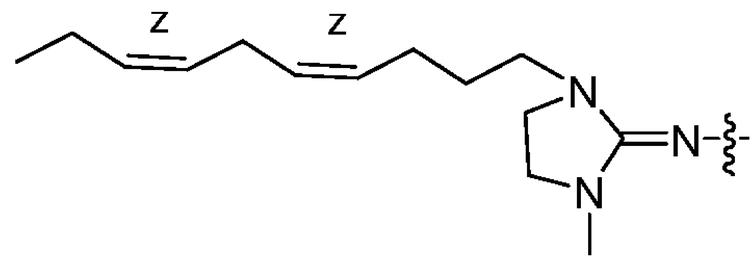
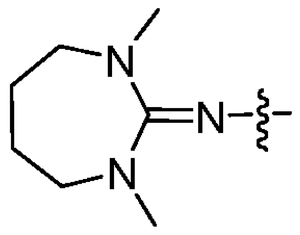
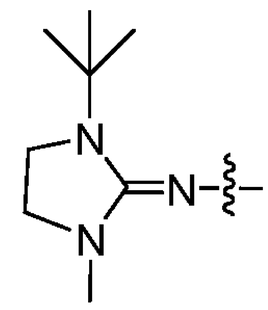
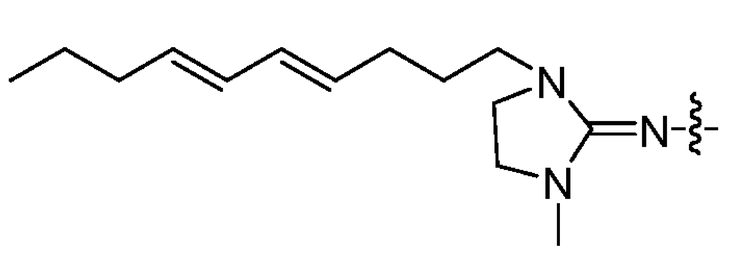
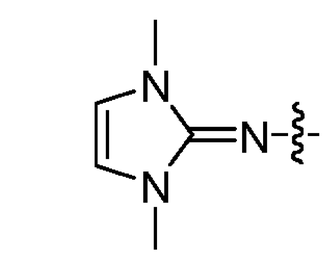
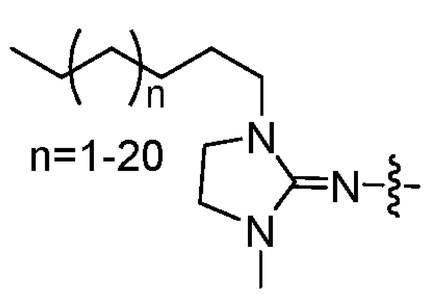
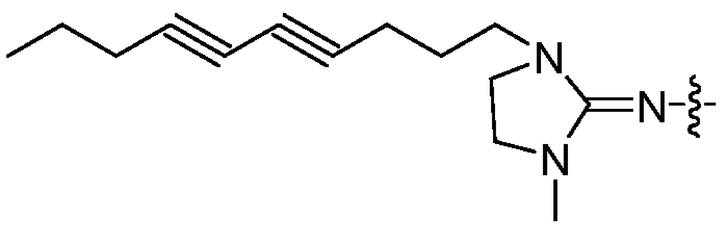
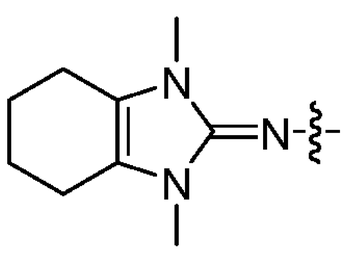
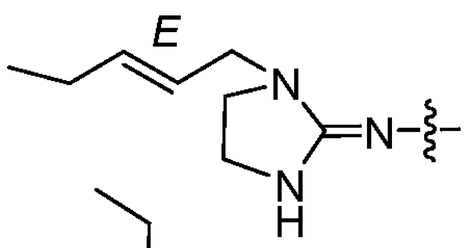
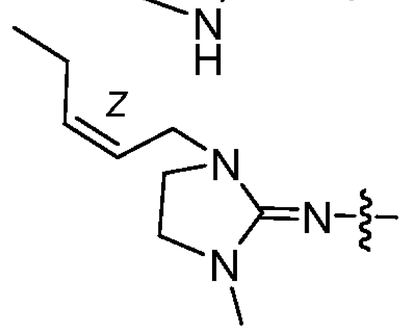
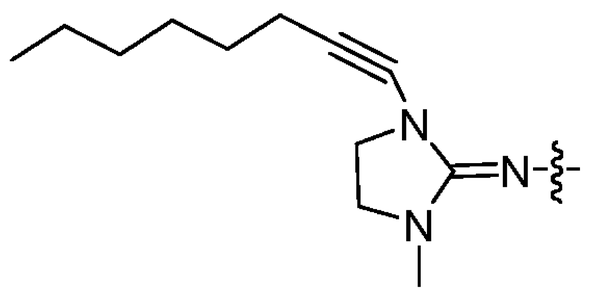
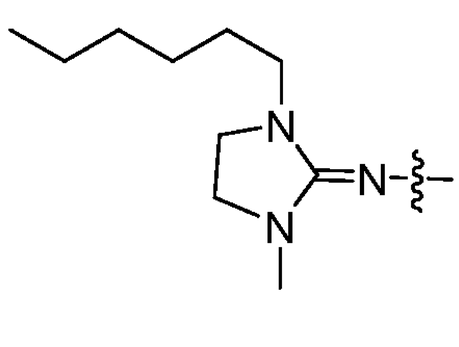
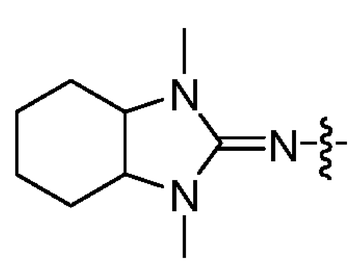
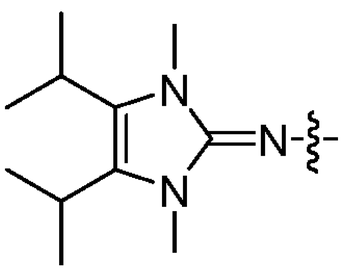
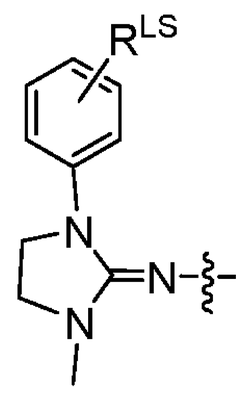
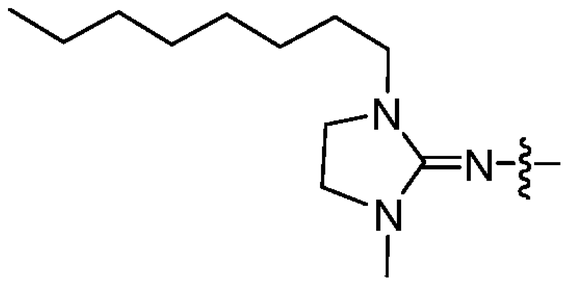
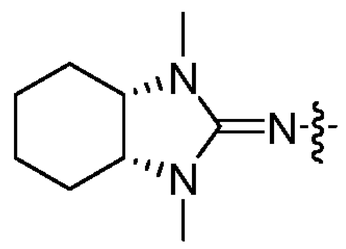
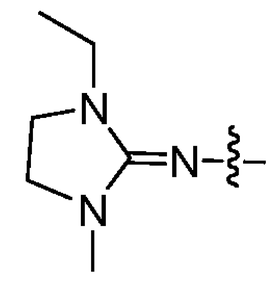
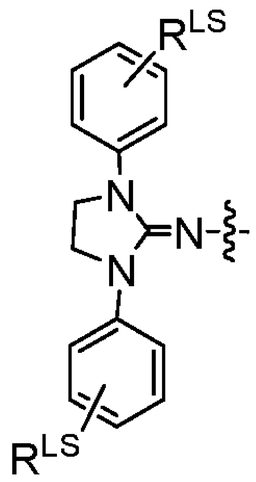
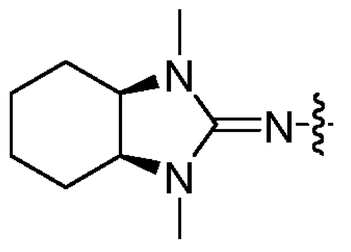
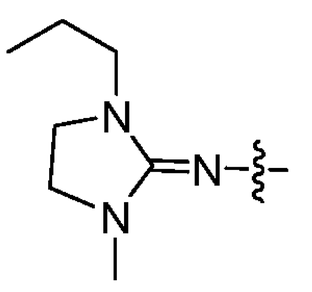
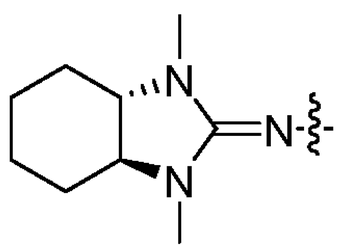
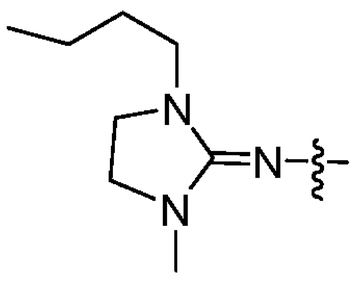
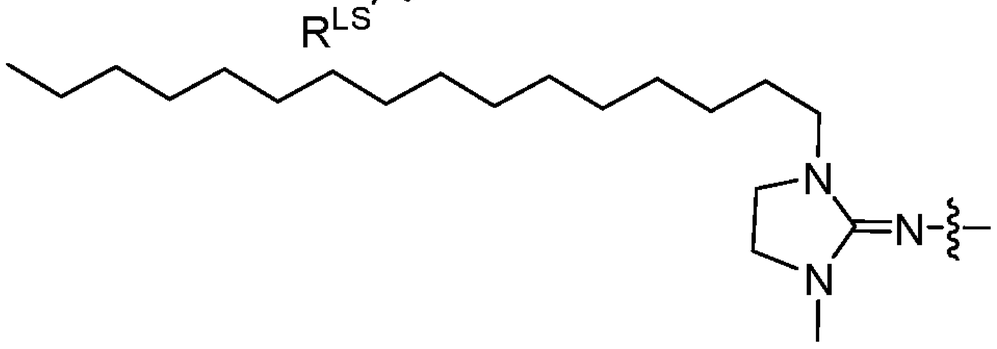
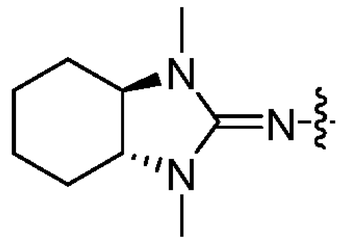
$-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  .

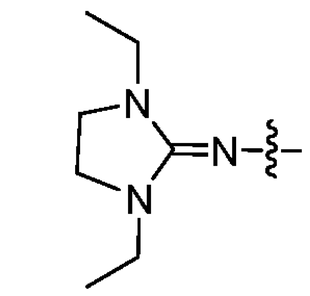
[00860] In some embodiments, $-X-R^L$ is R as described herein. In some embodiments, R is not hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl.

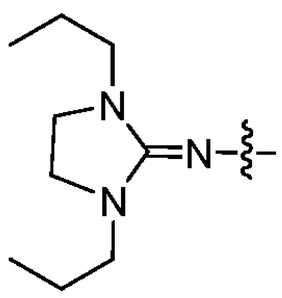
[00861] In some embodiments, $-X-R^L$ is selected from Tables below. In some embodiments, X is as described herein. In some embodiments, R^L is as described herein. In some embodiments, a linkage has the structure of $-Y-P^L(-X-R^L)-Z-$, wherein $-X-R^L$ is selected from Tables below, and each other variable is independently as described herein. In some embodiments, a linkage has the structure of or comprises $-P(O)(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-P(S)(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-P(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-P(O)(-X-R^L)-O-$, wherein $-X-R^L$

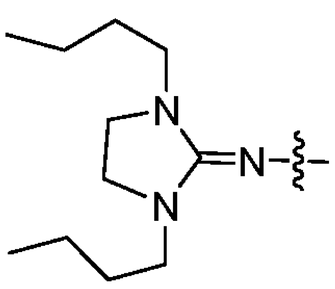
is selected from Tables below. In some embodiments, a linkage has the structure of or comprises −P(S)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of or comprises −P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −P(O)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −P(S)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, P is bonded to a nitrogen atom (e.g., a nitrogen atom in sm01, sm18, etc.). In some embodiments, a linkage has the structure of or comprises −O−P(O)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of or comprises −O−P(S)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of or comprises −O−P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(O)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(S)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, the Tables below, n is 0-20 or as described herein. As those skilled in the art appreciate, a linkage may exist in a salt form.

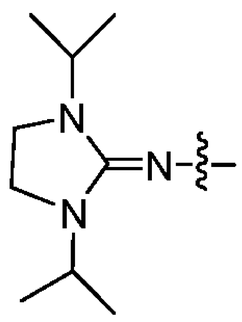
Table L-1. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).

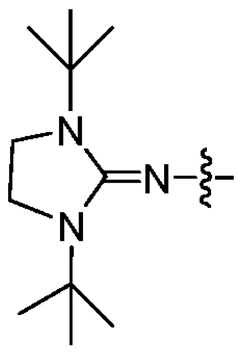




























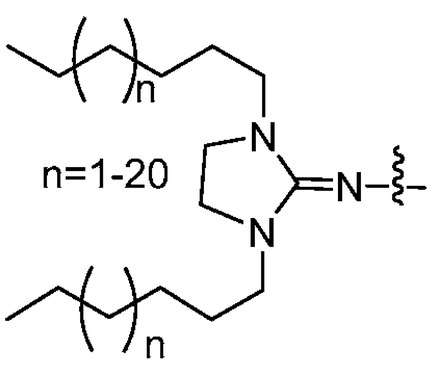


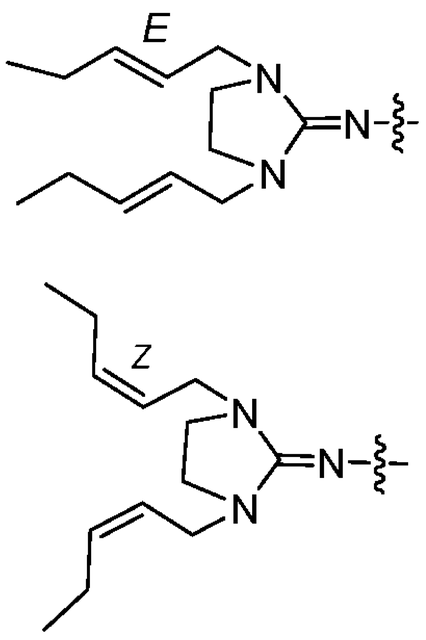


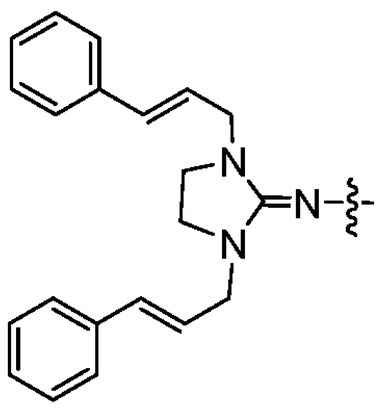


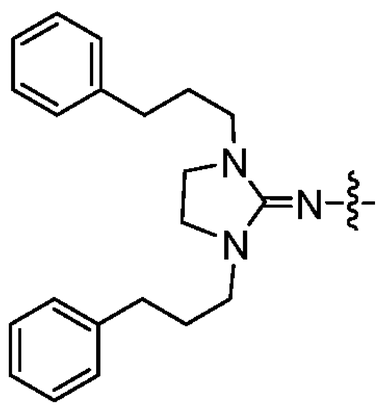


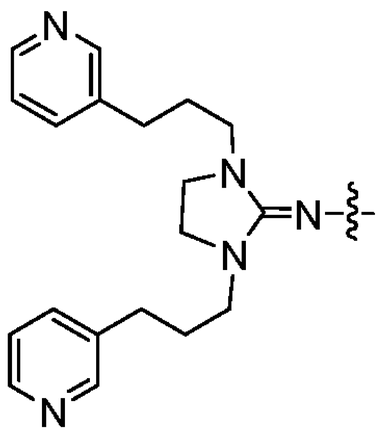


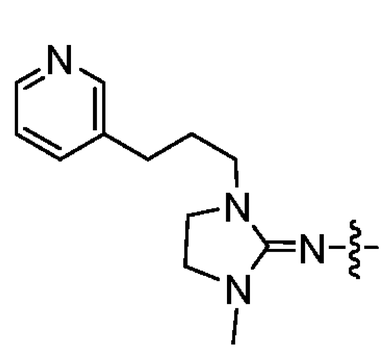

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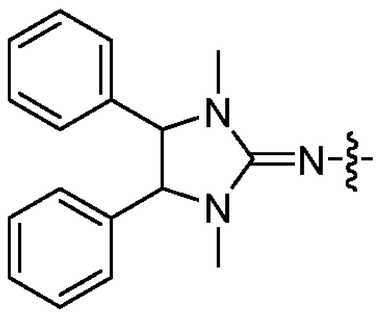

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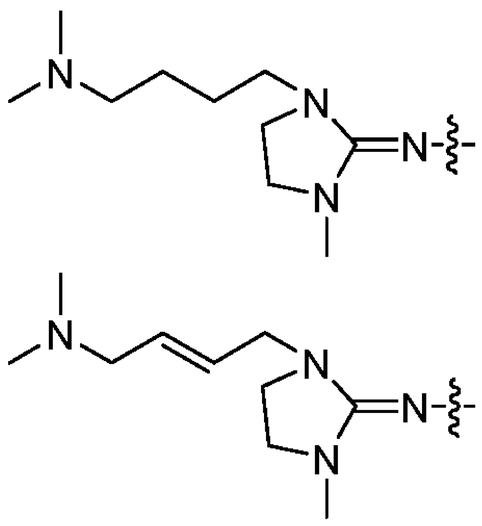


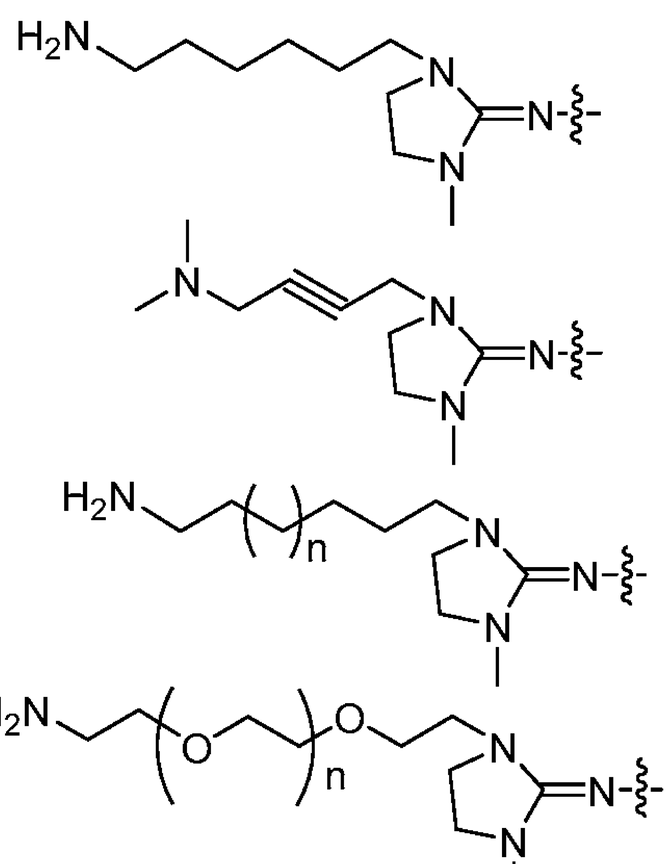


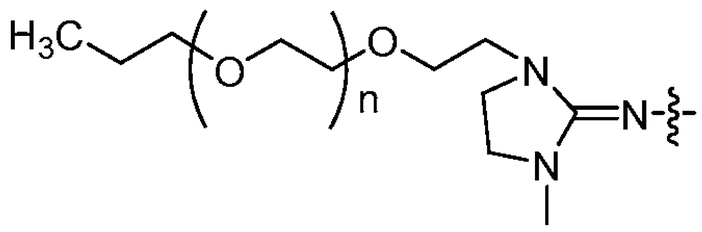


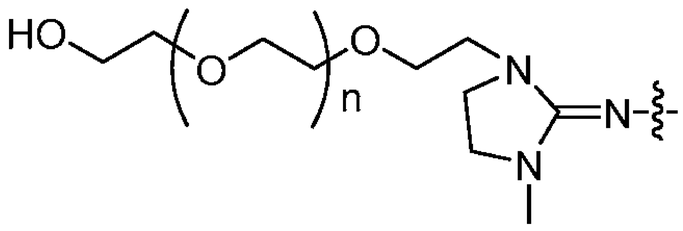


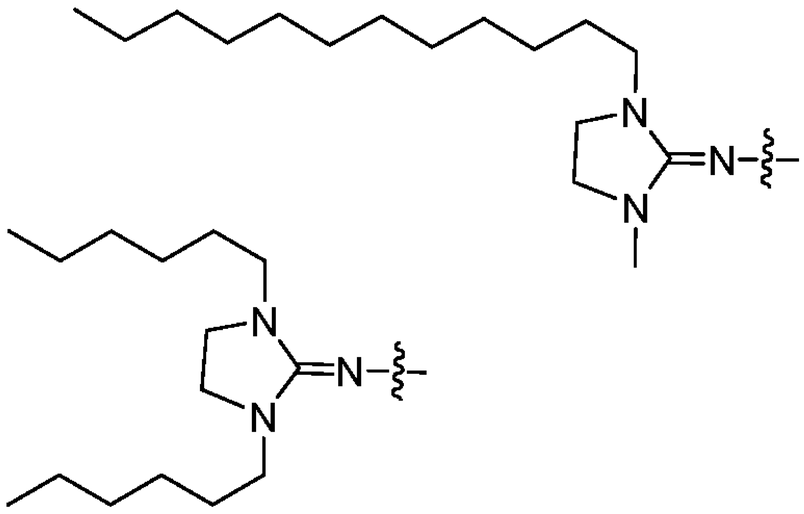


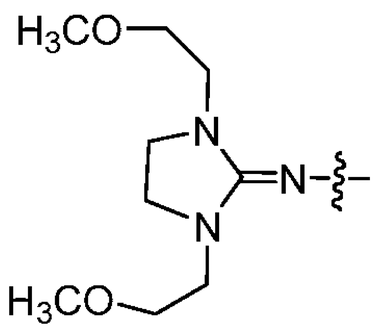


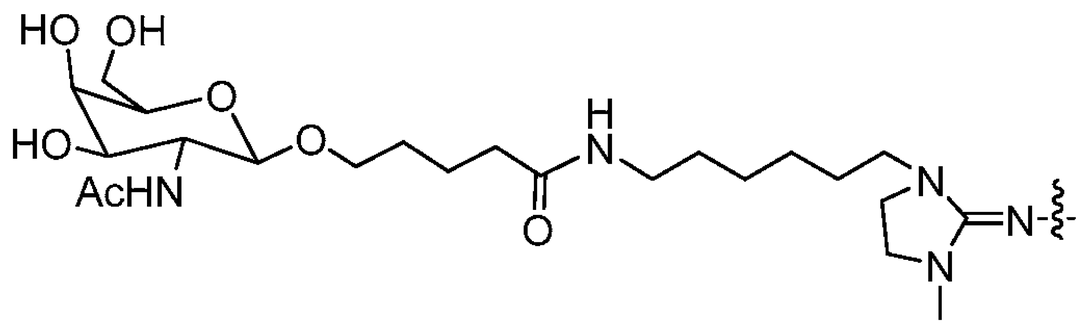

H2N
H2N
H2N
n
n
n

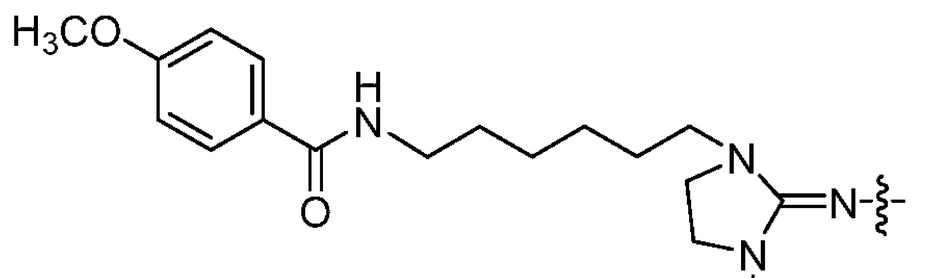

H3C
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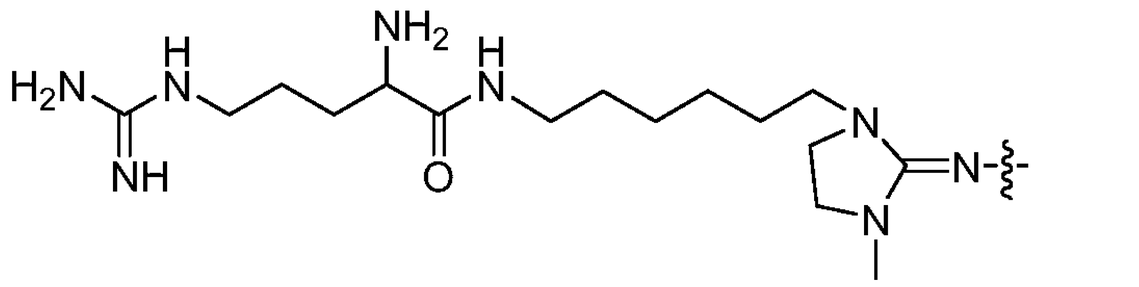

HO
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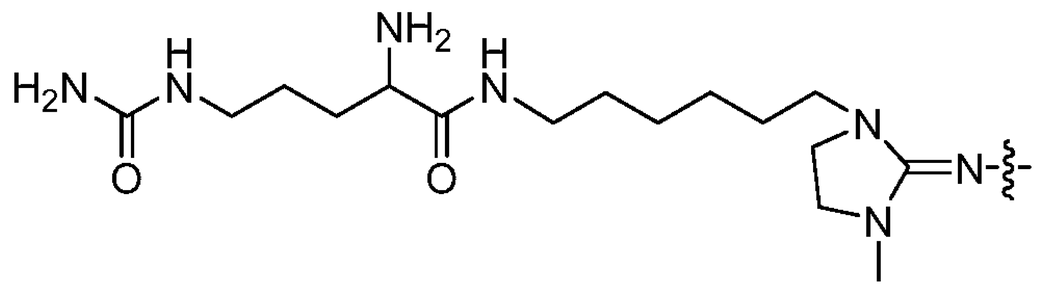


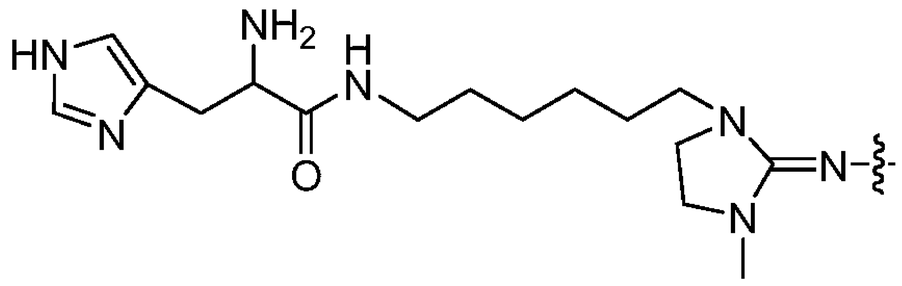

H3CO
H3CO

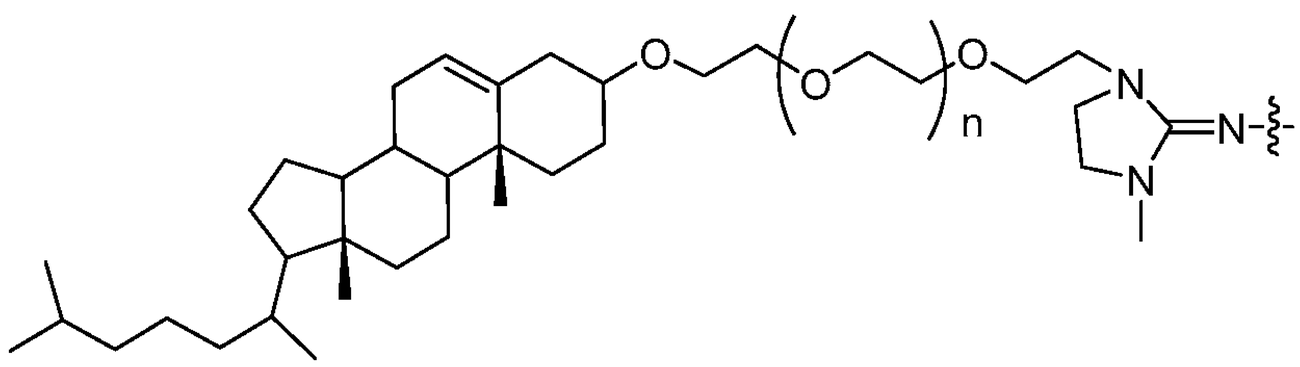


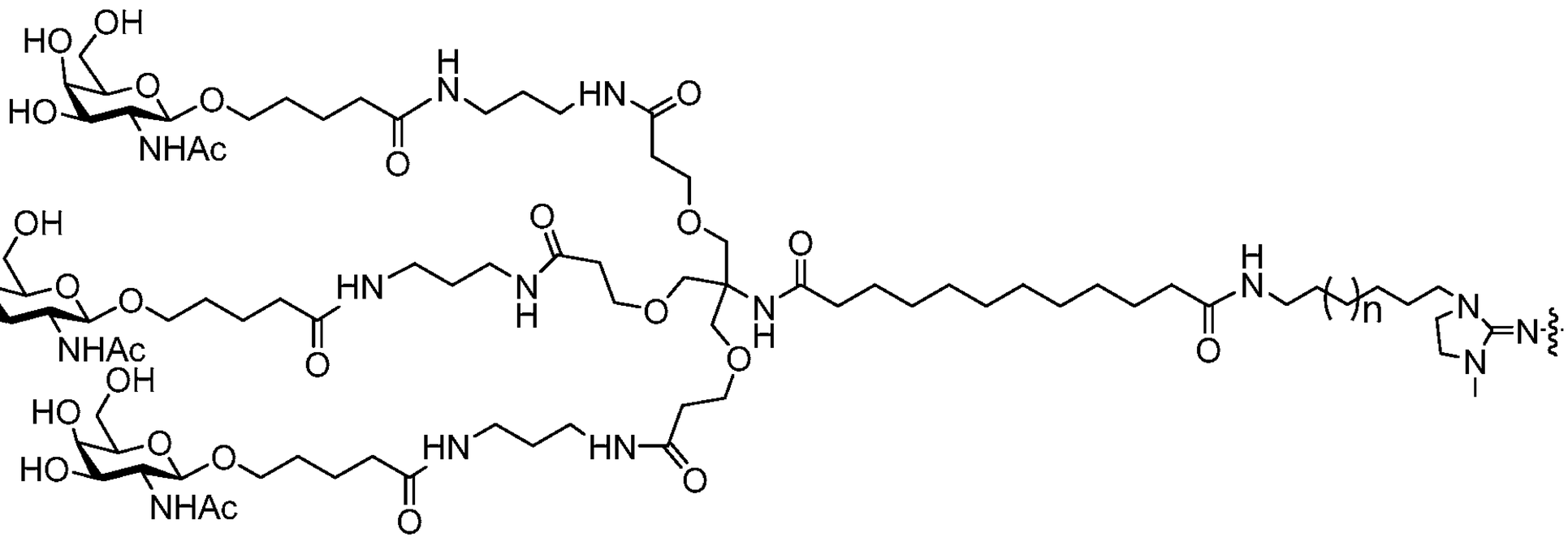








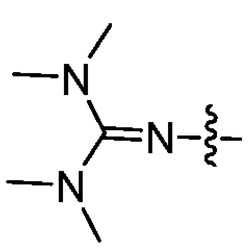


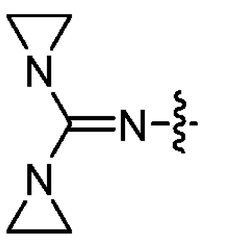


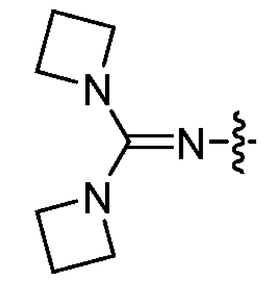
wherein each R^{LS} is independently R^s. In some embodiments, each R^{LS} is independently −Cl, −Br, −F,

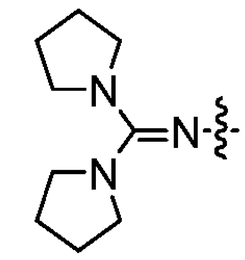
$-N(Me)_2$, or $-NHCOCH_3$.

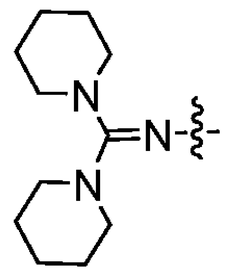
Table L-2. Certain useful moieties bonded to linkage phosphorus (e.g., $-X-R^L$).

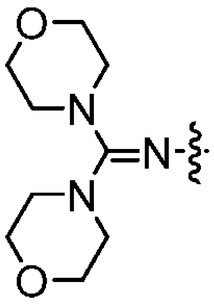


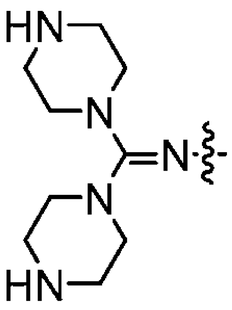


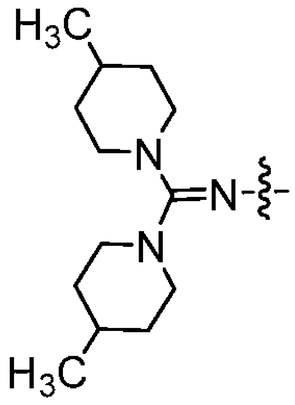


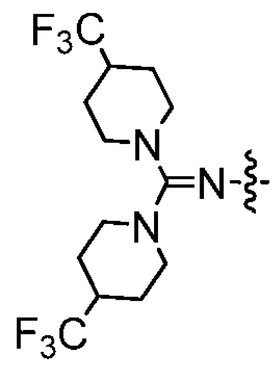


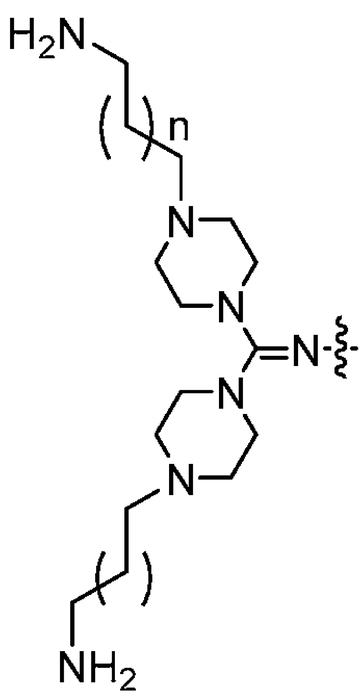


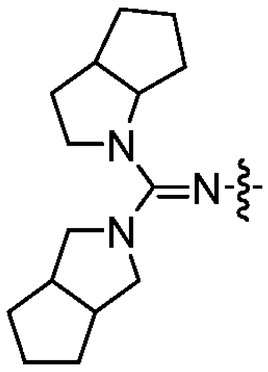


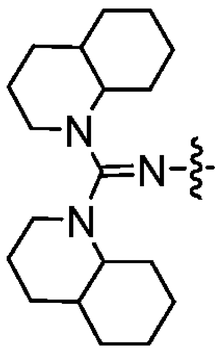


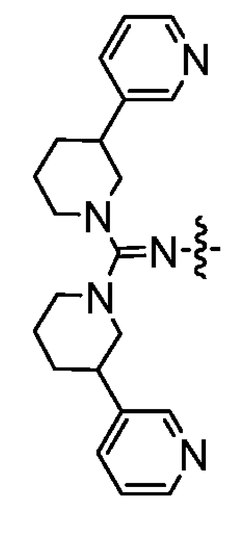


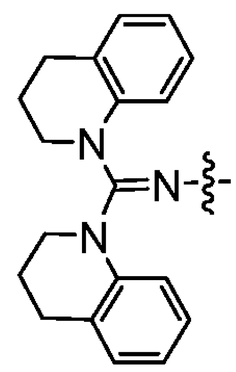


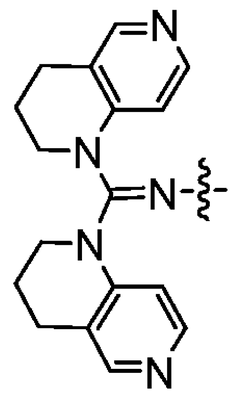












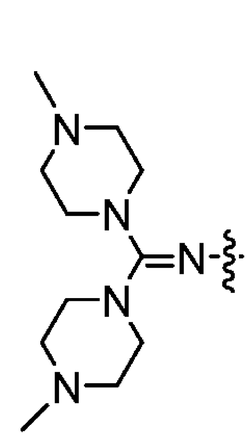


Table L-3. Certain useful moieties bonded to linkage phosphorus (e.g., $-X-R^L$).

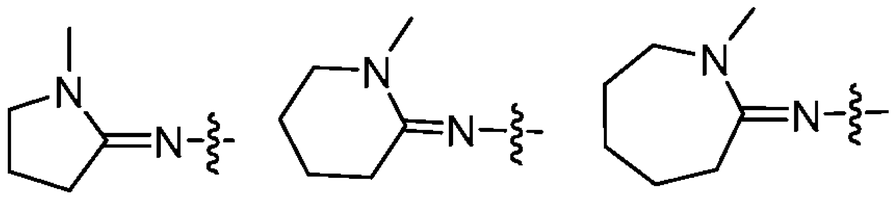
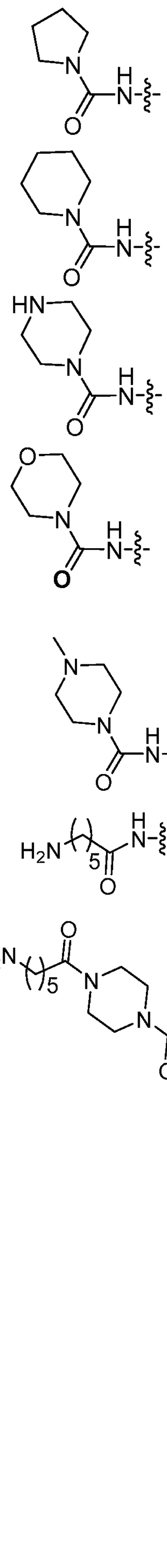
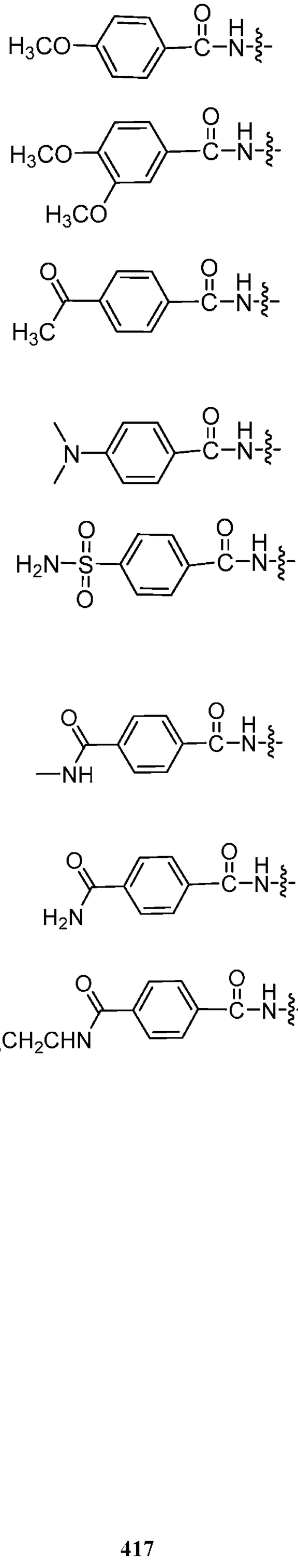
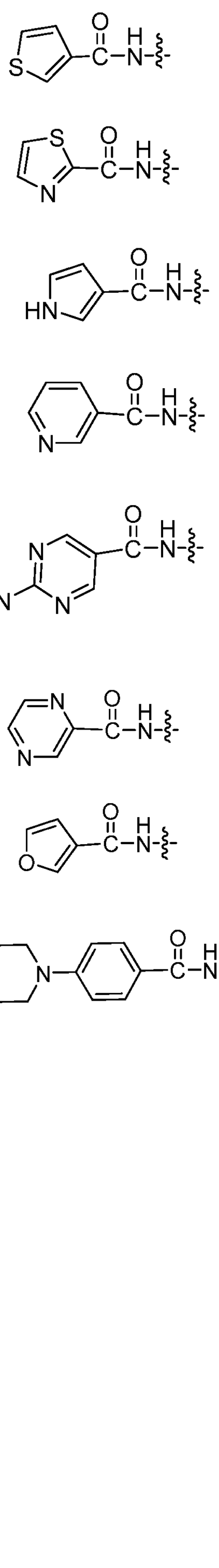


Table L-4. Certain useful moieties bonded to linkage phosphorus (e.g., $-X-R^L$).







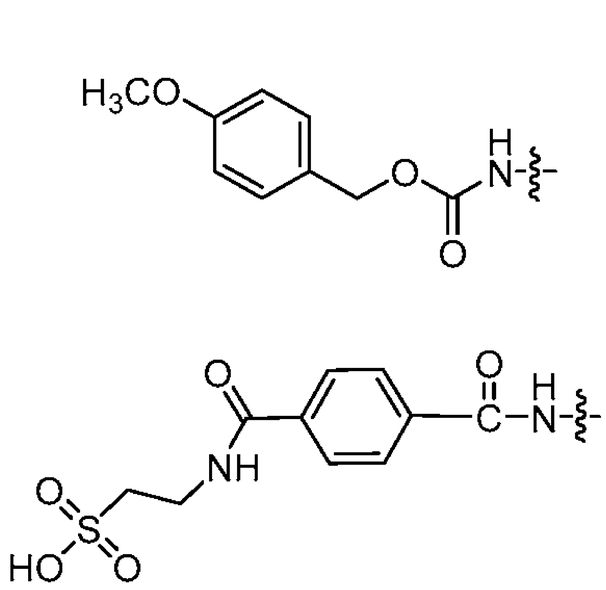
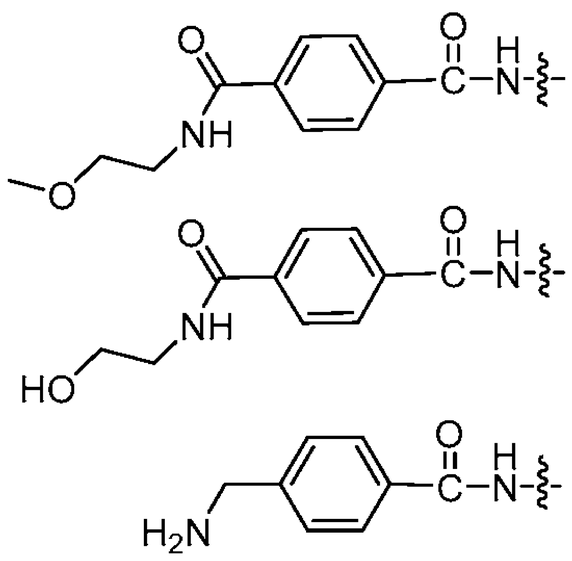
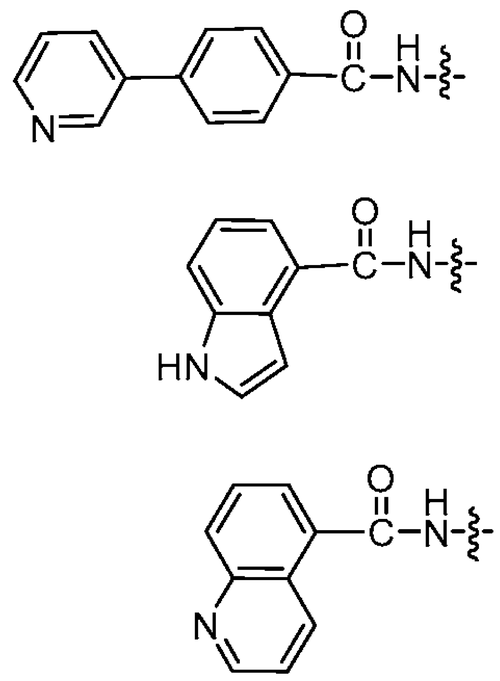
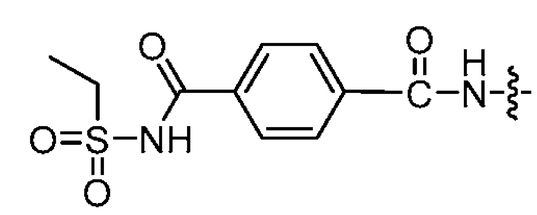
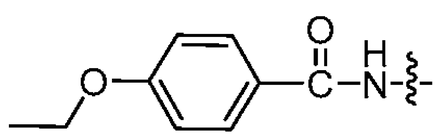
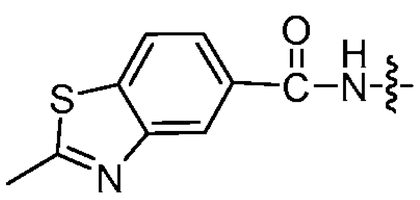
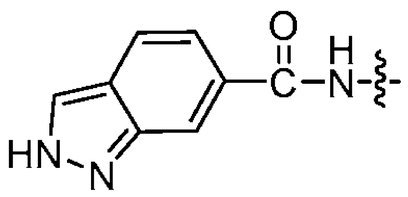
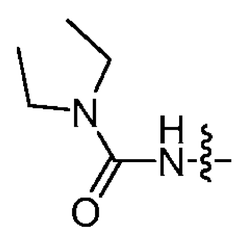
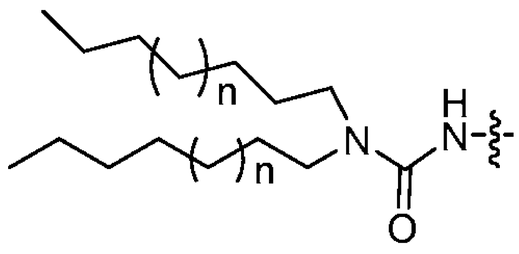
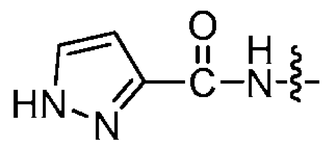
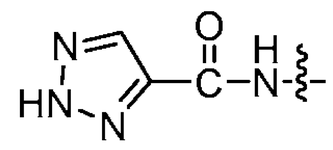
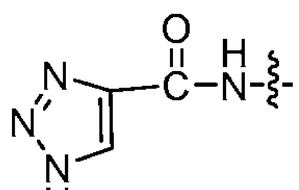
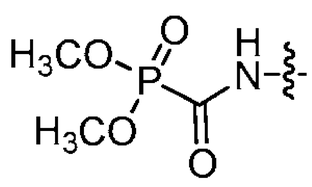
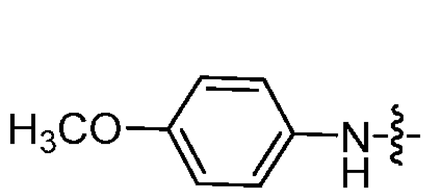
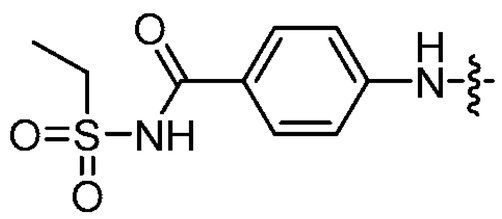
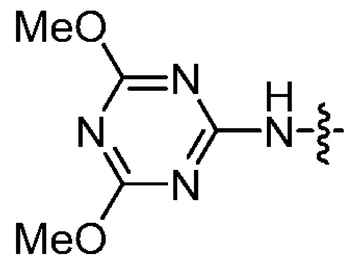
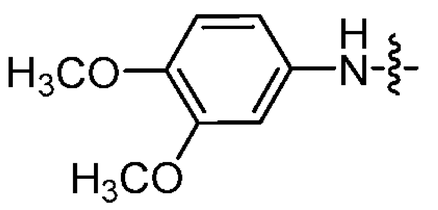
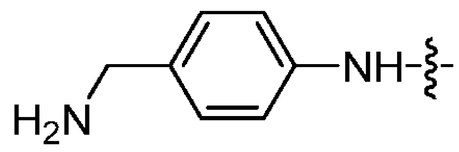
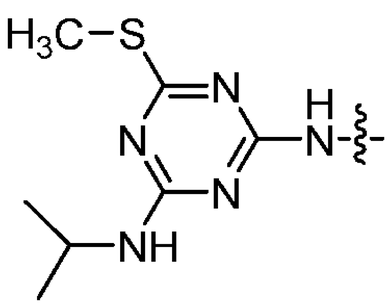
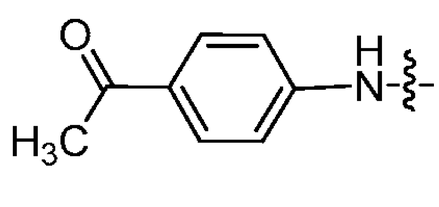
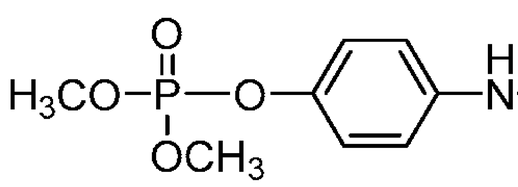
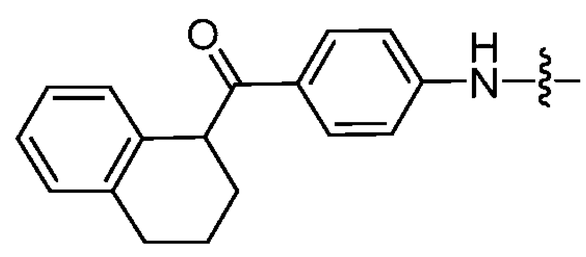
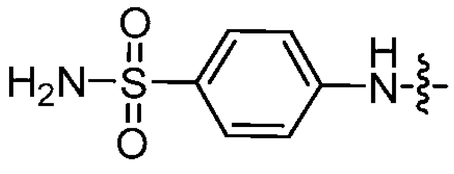
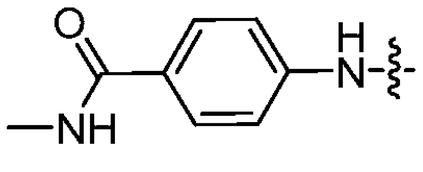
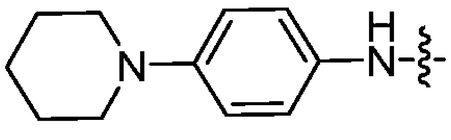














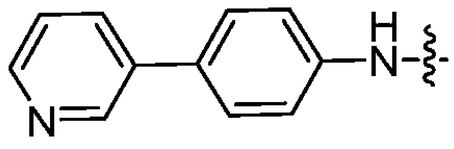
Table L-5. Certain useful moieties bonded to linkage phosphorus (e.g., $-X-R^L$).

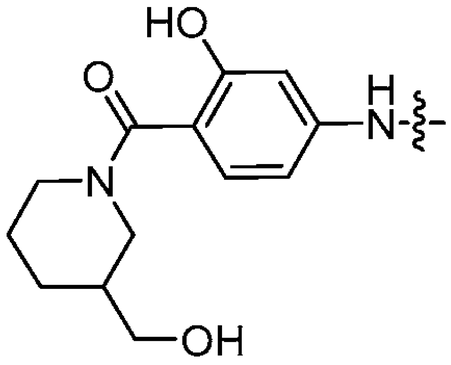










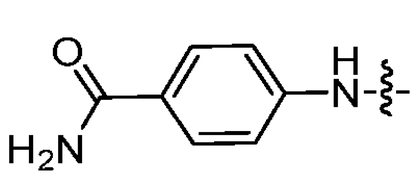


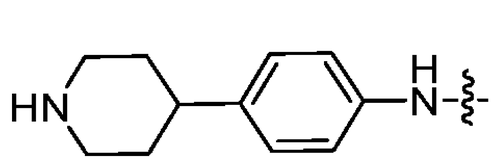


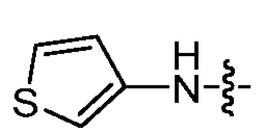


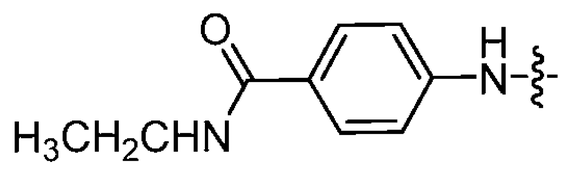


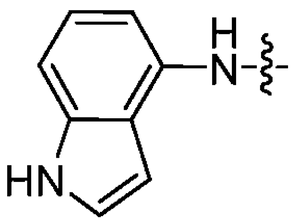


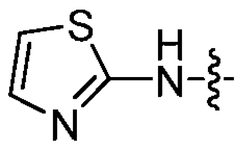


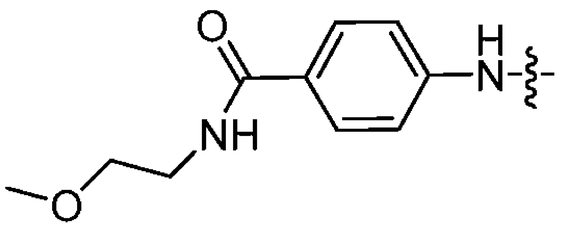


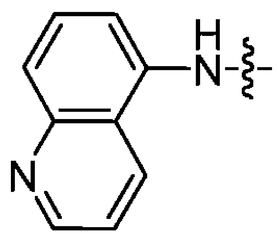


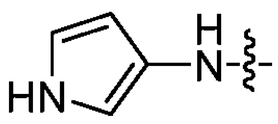


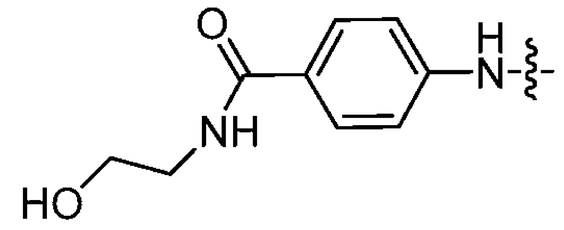


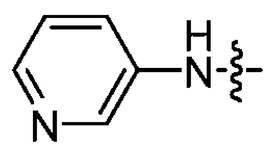


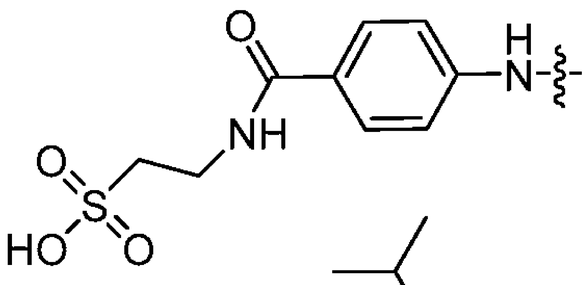


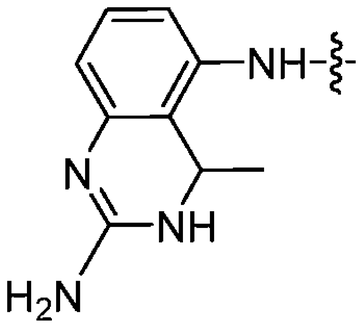


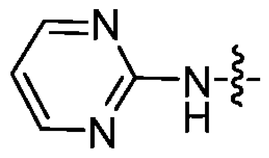


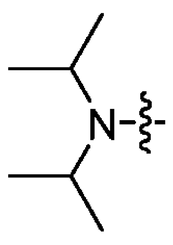


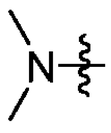


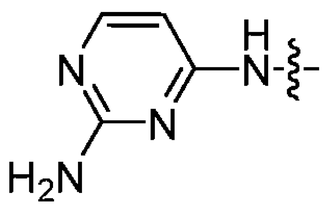


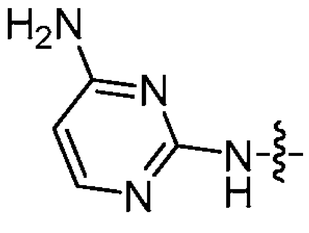


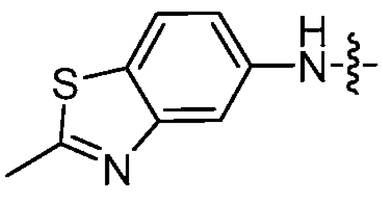


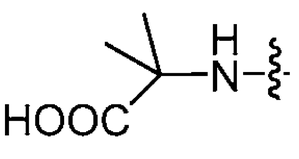


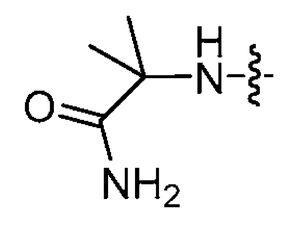


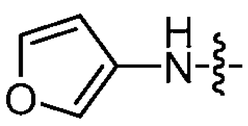


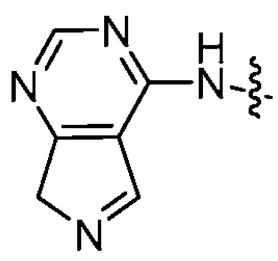


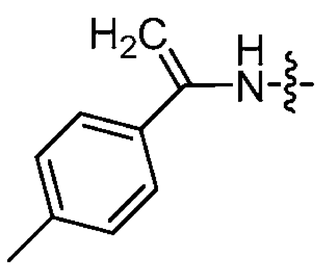


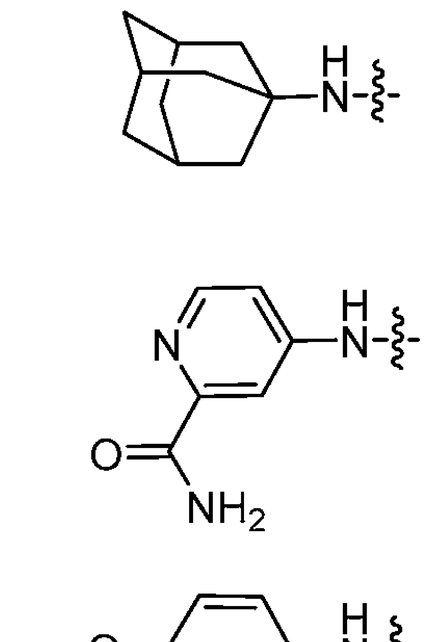


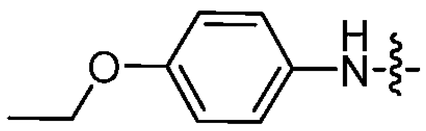


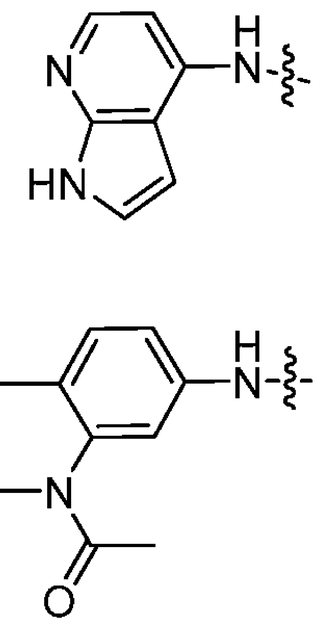


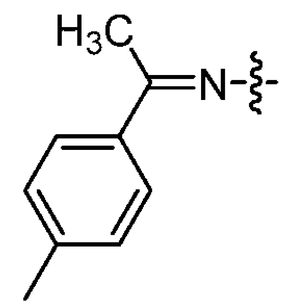


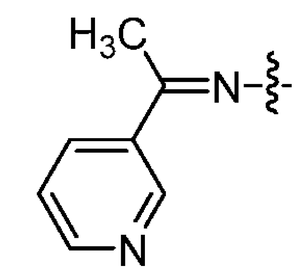


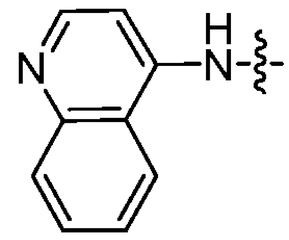


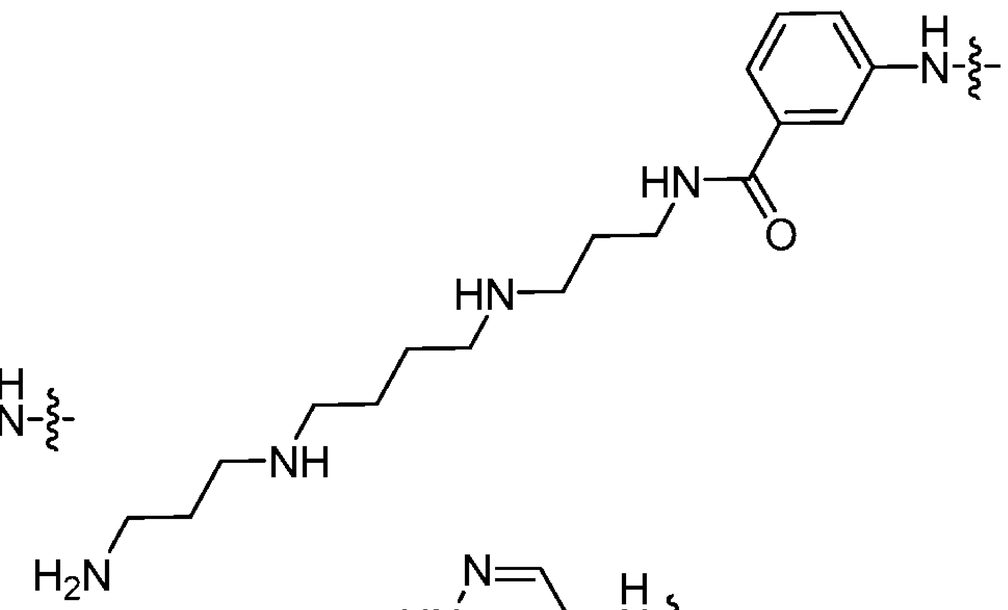


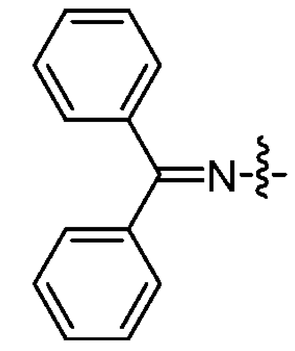


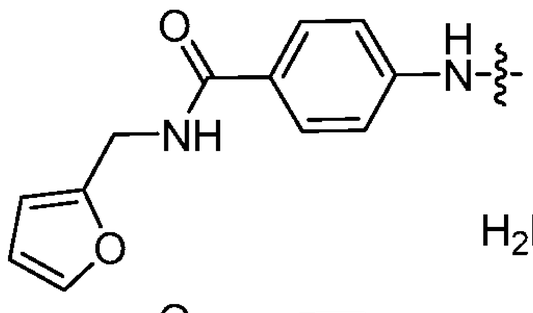


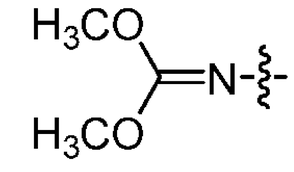


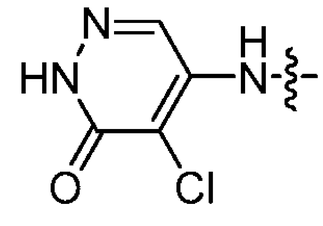












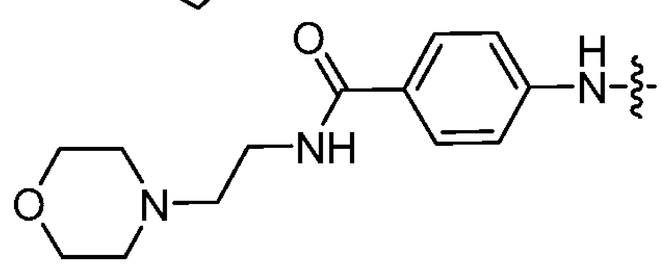
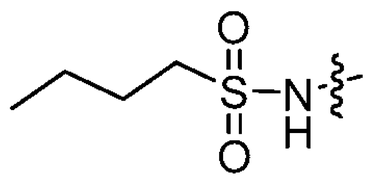
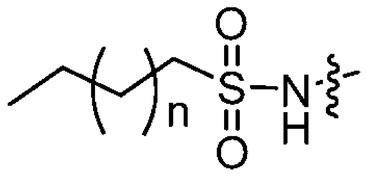
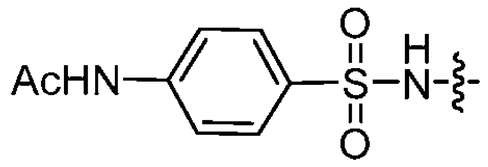
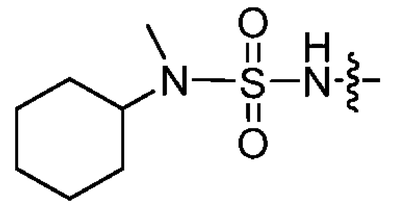


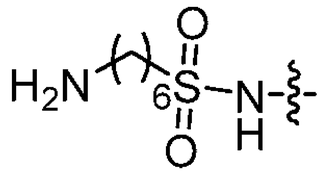
Table L-6. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).

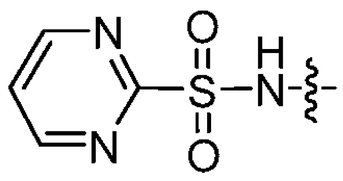


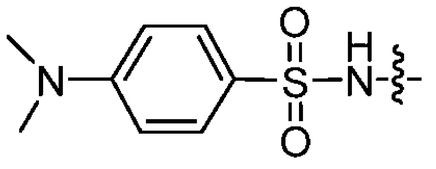


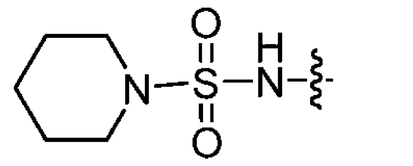


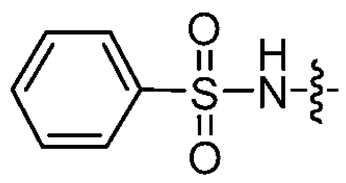


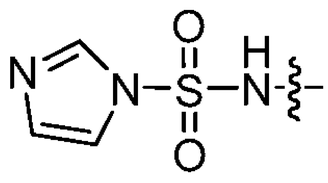


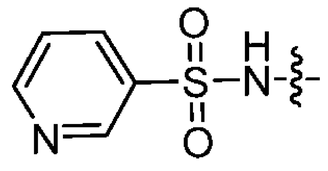


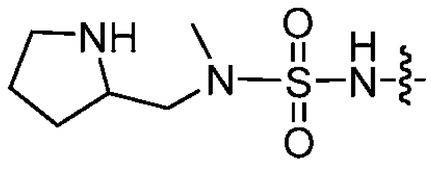


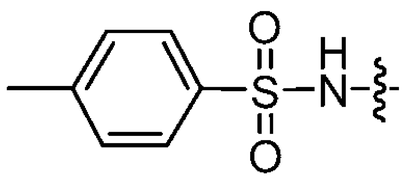


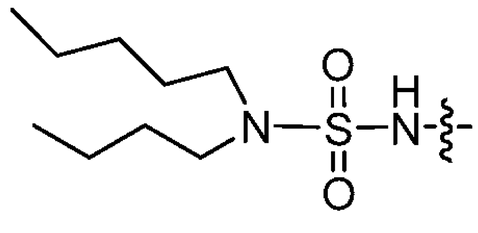


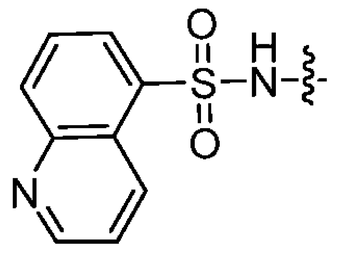




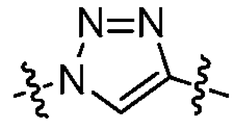
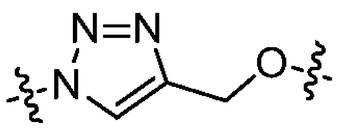








[00862] In some embodiments, an internucleotidic linkage, e.g., an non-negatively charged internucleotidic

linkage or a neutral internucleotidic linkage, has the structure of $-L^{L1}-Cy^{IL}-L^{L2}-$. In some embodiments, L^{L1} is bonded to a 3'-carbon of a sugar. In some embodiments, L^{L2} is bonded to a 5'-carbon of a sugar. In some embodiments, L^{L1} is $-O-CH_2-$. In some embodiments, L^{L2} is a covalent bond. In some embodiments, L^{L2} is a $-N(R')-$. In some embodiments, L^{L2} is a $-NH-$. In some embodiments, L^{L2} is bonded to a 5'-carbon of a sugar, which 5'-carbon is substituted with =O. In some embodiments, Cy^{IL} is optionally substituted 3-10 membered saturated, partially unsaturated, or aromatic ring having 0-5 heteroatoms. In some embodiments, Cy^{IL} is an optionally substituted triazole ring. In some embodiments, Cy^{IL} is  . In some embodiments, a linkage is  .

[00863] In some embodiments, a non-negatively charged internucleotidic linkage has the structure of $-OP(=W)(-N(R')_2)-O-$.

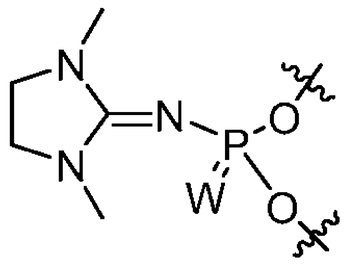
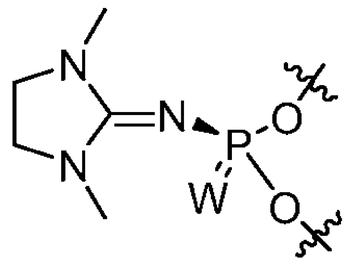
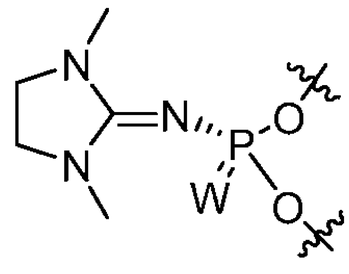
[00864] In some embodiments, R' is R. In some embodiments, R' is H. In some embodiments, R' is $-C(O)R$. In some embodiments, R' is $-C(O)OR$. In some embodiments, R' is $-S(O)_2R$.

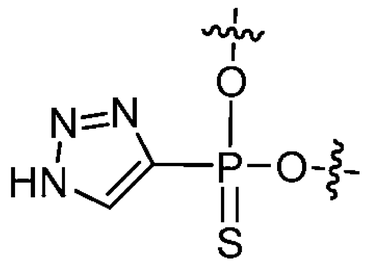
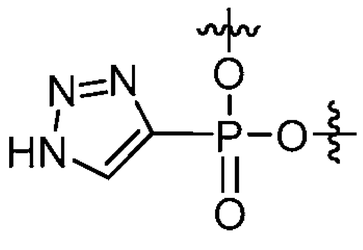
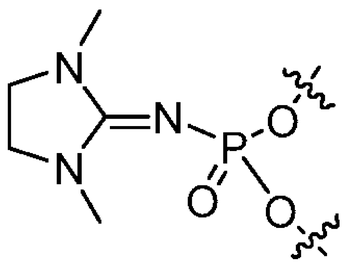
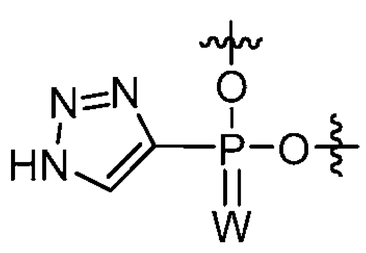
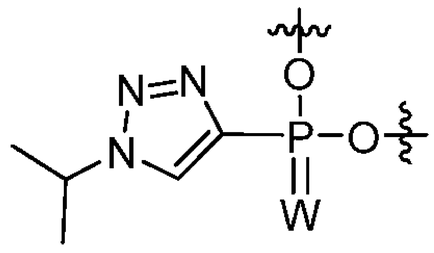
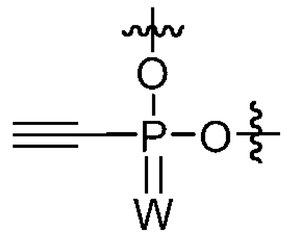
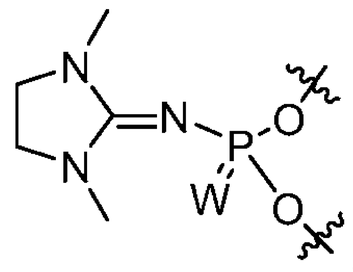
[00865] In some embodiments, R" is $-NHR'$. In some embodiments, $-N(R')_2$ is $-NHR'$.

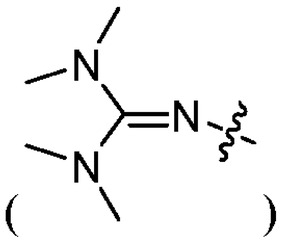
[00866] As described herein, some embodiments, R is H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is substituted methyl. In some embodiments, R is ethyl. In some embodiments, R is substituted ethyl.

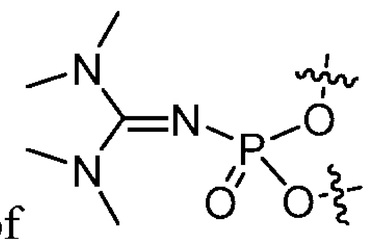
[00867] In some embodiments, as described herein, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage.

[00868] In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted triazolyl. In some embodiments, R' is or comprises optionally substituted triazolyl. In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted alkynyl. In some embodiments, R' is optionally substituted alkynyl. In some embodiments, R' comprises an optionally substituted triple bond. In some embodiments, a modified internucleotidic linkage comprises a triazole or alkyne moiety. In some embodiments, R' is or comprises an optionally substituted triazole or alkyne moiety. In some embodiments, a triazole moiety, e.g., a triazolyl group, is optionally substituted. In some embodiments, a triazole moiety, e.g., a triazolyl group) is substituted. In some embodiments, a triazole moiety is unsubstituted. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted guanidine moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$, is or comprises an optionally substituted guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$, is or comprises an optionally substituted cyclic guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$ comprises an optionally substituted cyclic guanidine moiety and an

internucleotidic linkage has the structure of:  ,  , or  , wherein W is O or S. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

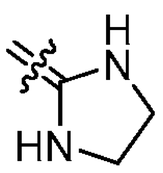
[00869] In some embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage is an internucleotidic linkage comprising a triazole moiety. In some embodiments, a non-negatively charged internucleotidic linkage or a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the structure of  . In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure selected from  ,  ,  ,  , or , wherein W is O or S.

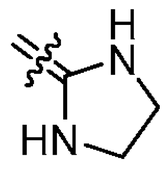
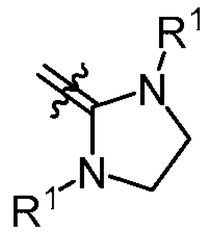
[00870] In some embodiments, an internucleotidic linkage comprises a Tmg group (). In some



embodiments, an internucleotidic linkage comprises a Tmg group and has the structure of (the "Tmg internucleotidic linkage"). In some embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and an Tmg internucleotidic linkage.

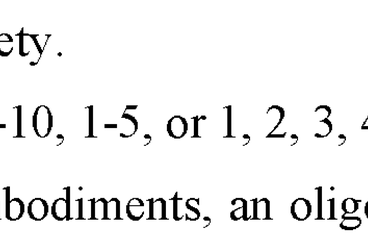
[00871] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, such a heterocyclyl or heteroaryl group is of a 5-membered ring. In some embodiments, such a heterocyclyl or heteroaryl group is of a 6-membered ring.

[00872] In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a heteroaryl group is directly bonded to a linkage phosphorus. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, at least two heteroatoms are nitrogen. In some embodiments, a heterocyclyl group is directly bonded to a linkage phosphorus. In some embodiments, a heterocyclyl group is bonded to a linkage phosphorus through a linker, e.g., =N− when the heterocyclyl group is part of a guanidine moiety who directed bonded to a linkage phosphorus through its =N−. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted  group. In some embodiments, a non-negatively charged

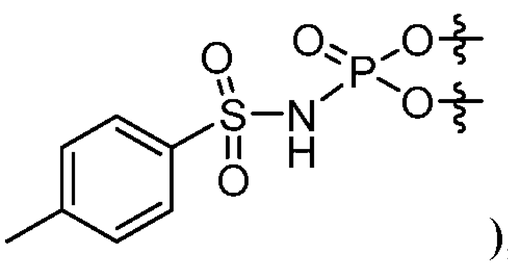
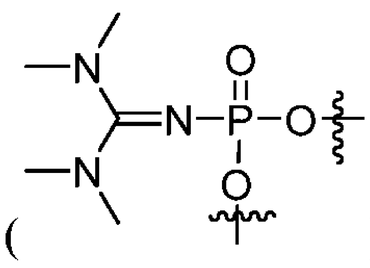
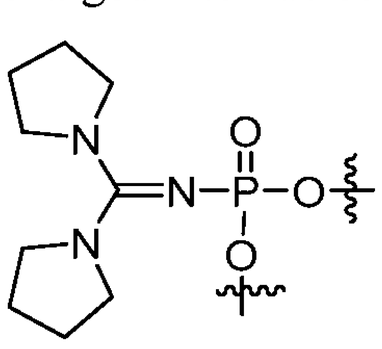
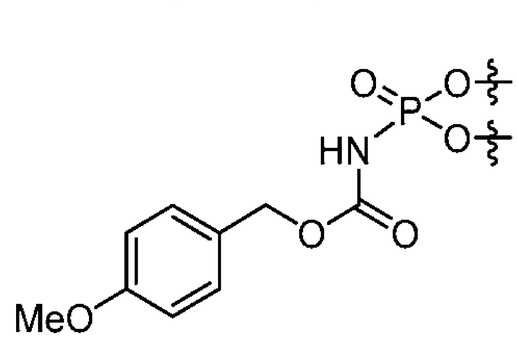
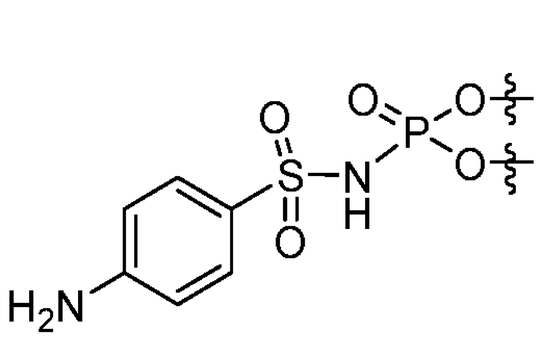
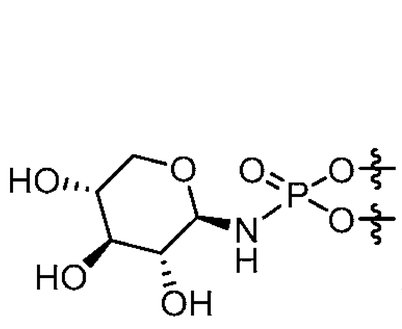
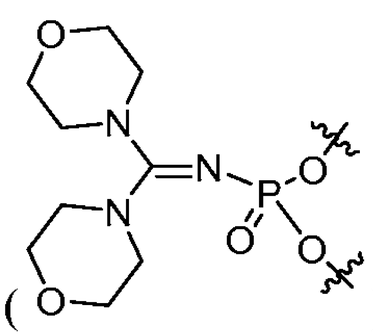
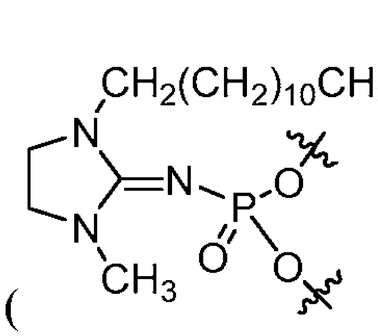
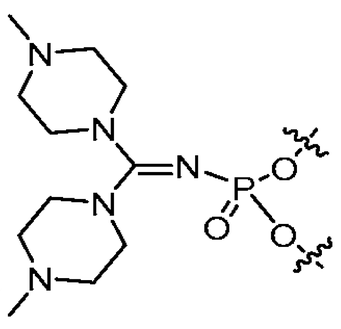
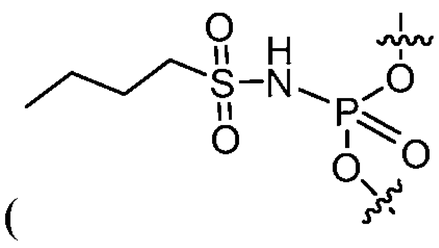
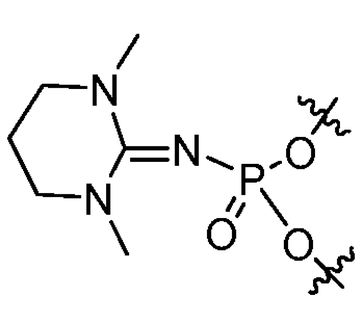
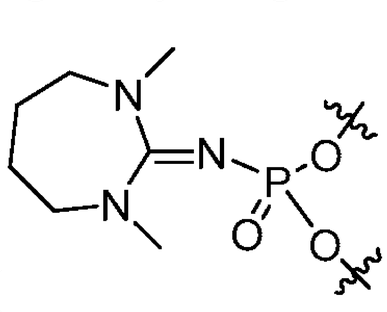
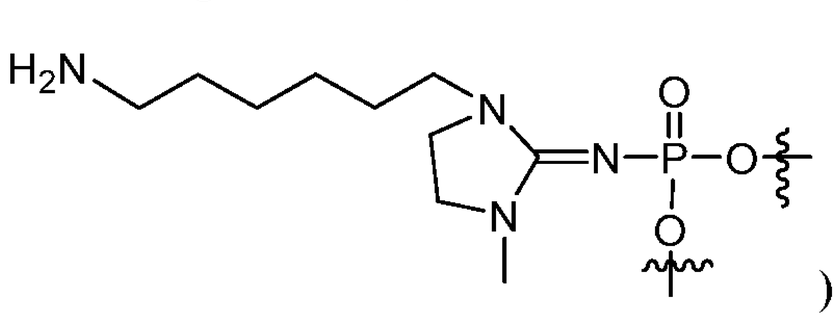
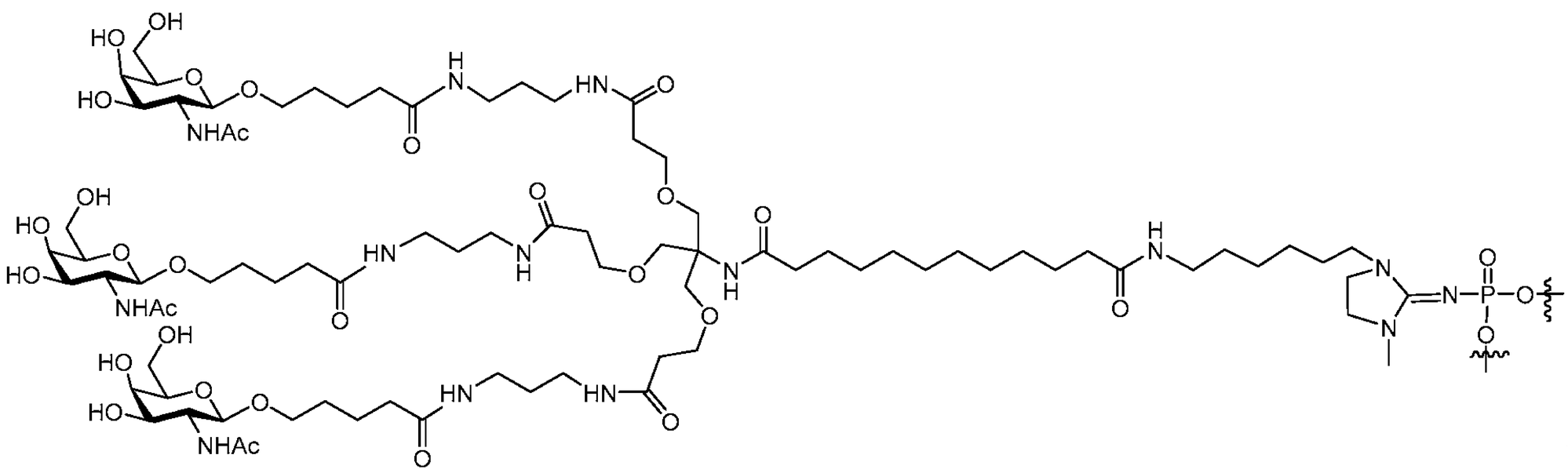
internucleotidic linkage comprises an substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises a  group. In some embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R^1 is independently methyl.

[00873] In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage is not chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is Rp. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is Sp.

[00874] In some embodiments, an internucleotidic linkage comprises no linkage phosphorus. In some embodiments, an internucleotidic linkage has the structure of −C(O)−(O)− or −C(O)−N(R')−, wherein R' is as described herein. In some embodiments, an internucleotidic linkage has the structure of −C(O)−(O)−. In some embodiments, an internucleotidic linkage has the structure of −C(O)−N(R')−, wherein R' is as described herein. In various embodiments, −C(O)− is bonded to nitrogen. In some embodiments, an internucleotidic linkage is or comprises −C(O)−O− which is part of a carbamate moiety. In some embodiments, an internucleotidic linkage is or comprises −C(O)−O− which is part of a urea moiety.

[00875] In some embodiments, an oligonucleotide comprises 1-20, 1-15, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more non-negatively charged internucleotidic linkages. In some embodiments, an oligonucleotide comprises 1-20, 1-15, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more neutral internucleotidic linkages. In some embodiments, each of non-negatively charged internucleotidic linkage and/or neutral internucleotidic linkages is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage in an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, each neutral internucleotidic linkage in an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, an oligonucleotide comprises at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in Rp configuration, and at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in Sp configuration.

[00876] In many embodiments, as demonstrated extensively, oligonucleotides of the present disclosure comprise two or more different internucleotidic linkages. In some embodiments, an oligonucleotide comprises

a phosphorothioate internucleotidic linkage and a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, a non-negatively charged internucleotidic linkage, and a natural phosphate linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001, n002 (), n003 (), n004 (), n005 (), n006 (), n007 (), n008 (), n009 (), n010 (), or n013. In some embodiments, a non-negatively charged internucleotidic linkage is n020 (), n025 (), n026 (), n051 () or n057 (). In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, each chiral modified internucleotidic linkage is independently chirally controlled. In some embodiments, one or more non-negatively charged internucleotidic linkage are not chirally controlled.

[00877] A typical connection, as in natural DNA and RNA, is that an internucleotidic linkage forms bonds with two sugars (which can be either unmodified or modified as described herein). In many embodiments, as exemplified herein an internucleotidic linkage forms bonds through its oxygen atoms or heteroatoms with one optionally modified ribose or deoxyribose at its 5' carbon, and the other optionally modified ribose or deoxyribose at its 3' carbon. In some embodiments, internucleotidic linkages connect sugars that are not ribose sugars, e.g., sugars comprising N ring atoms and acyclic sugars as described herein.

[00878] In some embodiments, each nucleoside units connected by an internucleotidic linkage independently comprises a nucleobase which is independently an optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G or U.

[00879] In some embodiments, an oligonucleotide comprises a modified internucleotidic linkage (e.g., a modified internucleotidic linkage having the structure of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof) as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612 the internucleotidic linkages (e.g., those of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.,) of each of which are independently incorporated herein by reference. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, the present disclosure provides oligonucleotides comprising one or more neutral internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage (e.g., one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.) is as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612. In some embodiments, a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage is one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. as described in WO 2018/223056, WO 2019/032607, WO 2019/075357, WO 2019/032607, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, such internucleotidic linkages of each of which are independently incorporated herein by reference.

[00880] As described herein, various variables can be R, e.g., R', R^L, etc. Various embodiments for R are

described in the present disclosure (e.g., when describing variables that can be R). Such embodiments are generally useful for all variables that can be R. In some embodiments, R is hydrogen. In some embodiments, R is optionally substituted C_{1-30} (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) aliphatic. In some embodiments, R is optionally substituted C_{1-20} aliphatic. In some embodiments, R is optionally substituted C_{1-10} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted alkyl. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted propyl. In some embodiments, R is isopropyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is optionally substituted pentyl. In some embodiments, R is optionally substituted hexyl.

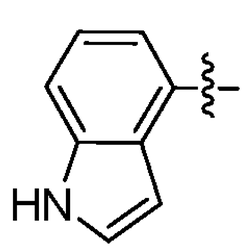
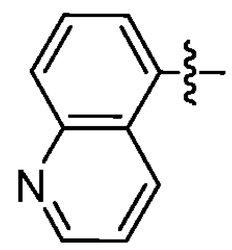
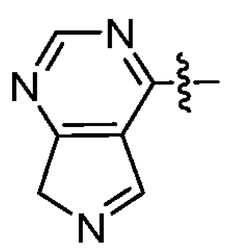
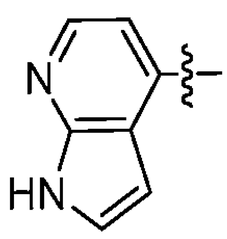
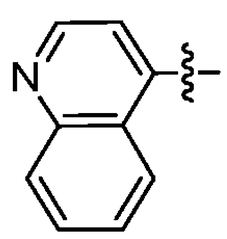
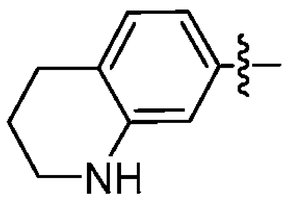
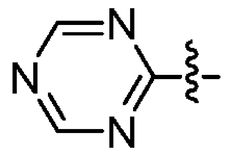
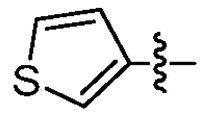
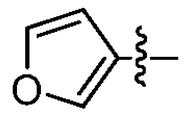
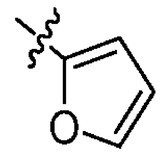
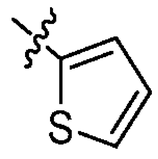
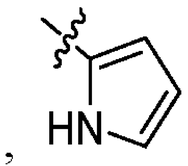
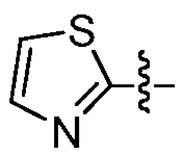
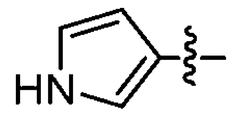
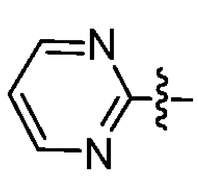
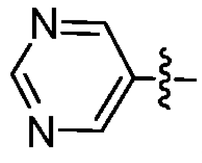
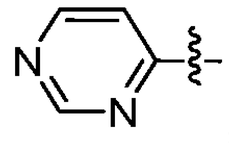
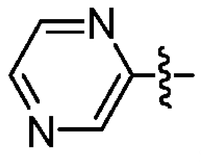
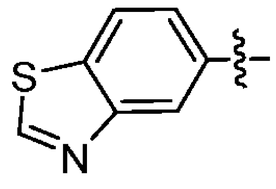
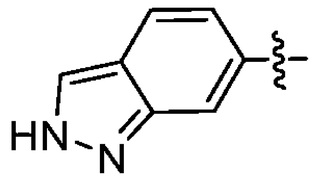
[00881] In some embodiments, R is optionally substituted 3-30 membered (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) cycloaliphatic. In some embodiments, R is optionally substituted cycloalkyl. In some embodiments, cycloaliphatic is monocyclic, bicyclic, or polycyclic, wherein each monocyclic unit is independently saturated or partially saturated. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is optionally substituted adamantyl.

[00882] In some embodiments, R is optionally substituted C_{1-30} (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) heteroaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-20} aliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-10} aliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-6} aliphatic having 1-3 heteroatoms. In some embodiments, R is optionally substituted heteroalkyl. In some embodiments, R is optionally substituted C_{1-6} heteroalkyl. In some embodiments, R is optionally substituted 3-30 membered (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) heterocycloaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted heteroclycloalkyl. In some embodiments, heterocycloaliphatic is monocyclic, bicyclic, or polycyclic, wherein each monocyclic unit is independently saturated or partially saturated.

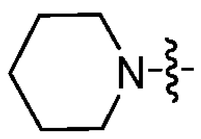
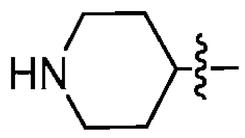
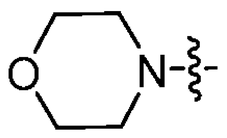
[00883] In some embodiments, R is optionally substituted C_{6-30} aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is C_{6-14} aryl. In some embodiments, R is optionally substituted bicyclic aryl. In some embodiments, R is optionally substituted polycyclic aryl. In some embodiments, R is optionally substituted C_{6-30} arylaliphatic. In some embodiments, R is C_{6-30} arylheteroaliphatic having 1-10 heteroatoms.

[00884] In some embodiments, R is optionally substituted 5-30 (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-20 membered heteroaryl having 1-10 heteroatoms. In some

embodiments, R is optionally substituted 5-10 membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having one heteroatom. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having one heteroatom. In some embodiments, R is optionally substituted monocyclic heteroaryl. In some embodiments, R is optionally substituted bicyclic heteroaryl. In some embodiments, R is optionally substituted polycyclic heteroaryl. In some embodiments, a heteroatom is nitrogen.

[00885] In some embodiments, R is optionally substituted 2-pyridinyl. In some embodiments, R is optionally substituted 3-pyridinyl. In some embodiments, R is optionally substituted 4-pyridinyl. In some embodiments, R is optionally substituted  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[00886] In some embodiments, R is optionally substituted 3-30 (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 3-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 4-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-20 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-10 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having one heteroatom. In some

embodiments, R is optionally substituted 6-membered heterocyclyl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having one heteroatom. In some embodiments, R is optionally substituted monocyclic heterocyclyl. In some embodiments, R is optionally substituted bicyclic heterocyclyl. In some embodiments, R is optionally substituted polycyclic heterocyclyl. In some embodiments, R is optionally substituted saturated heterocyclyl. In some embodiments, R is optionally substituted partially unsaturated heterocyclyl. In some embodiments, a heteroatom is nitrogen. In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  .

[00887] In some embodiments, two R groups are optionally and independently taken together to form a covalent bond. In some embodiments, two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

[00888] Various variables may comprises an optionally substituted ring, or can be taken together with their intervening atom(s) to form a ring. In some embodiments, a ring is 3-30 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered. In some embodiments, a ring is 3-20 membered. In some embodiments, a ring is 3-15 membered. In some embodiments, a ring is 3-10 membered. In some embodiments, a ring is 3-8 membered. In some embodiments, a ring is 3-7 membered. In some embodiments, a ring is 3-6 membered. In some embodiments, a ring is 4-20 membered. In some embodiments, a ring is 5-20 membered. In some embodiments, a ring is monocyclic. In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, each monocyclic ring or each monocyclic ring unit in bicyclic or polycyclic rings is independently saturated, partially saturated or aromatic. In some embodiments, each monocyclic ring or each monocyclic ring unit in bicyclic or polycyclic rings is independently 3-10 membered and has 0-5 heteroatoms.

[00889] In some embodiments, each heteroatom is independently selected oxygen, nitrogen, sulfur, silicon, and phosphorus. In some embodiments, each heteroatom is independently selected oxygen, nitrogen, sulfur, and phosphorus. In some embodiments, each heteroatom is independently selected oxygen, nitrogen, and sulfur. In some embodiments, a heteroatom is in an oxidized form.

[00890] As appreciated by those skilled in the art, many other types of internucleotidic linkages may be utilized in accordance with the present disclosure, for example, those described in U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,177,195; 5,023,243; 5,034,506; 5,166,315; 5,185,444; 5,188,897; 5,214,134; 5,216,141; 5,235,033; 5,264,423; 5,264,564; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,938; 5,405,939; 5,434,257; 5,453,496; 5,455,233; 5,466,677; 5,466,677; 5,470,967; 5,476,925; 5,489,677; 5,519,126; 5,536,821; 5,541,307; 5,541,316; 5,550,111; 5,561,225; 5,563,253; 5,571,799; 5,587,361; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,625,050; 5,633,360; 5,64,562; 5,663,312; 5,677,437; 5,677,439; 6,160,109; 6,239,265; 6,028,188; 6,124,445; 6,169,170; 6,172,209; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; or RE39464. In some embodiments, a modified internucleotidic linkage is one described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the nucleobases, sugars, internucleotidic linkages, chiral auxiliaries/reagents, and technologies for oligonucleotide synthesis (reagents, conditions, cycles, etc.) of each of which is independently incorporated herein by reference.

[00891] In some embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a non-negatively charged internucleotidic linkage (e.g., n001, n002, n003, n004, n005, n006, n007, n008, n009, n010, n013, etc.). In some embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a neutral internucleotidic linkage (e.g., n001, n002, n003, n004, n005, n006, n007, n008, n009, n010, n013, etc.).

[00892] Oligonucleotides can comprise various numbers of natural phosphate linkages, e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more. In some embodiments, one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) of the natural phosphate linkages in an oligonucleotide are consecutive. In some embodiments, provided oligonucleotides comprise no natural phosphate linkages. In some embodiments, provided oligonucleotides comprise one natural phosphate linkage. In some embodiments, provided oligonucleotides comprise 1 to 30 or more natural phosphate linkages.

[00893] In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage which comprises a chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled with respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is stereochemically pure with

respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is not chirally controlled. In some embodiments, a pattern of backbone chiral centers comprises or consists of positions and linkage phosphorus configurations of chirally controlled internucleotidic linkages (*R*p or *S*p) and positions of achiral internucleotidic linkages (e.g., natural phosphate linkages).

[00894] In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more neutral internucleotidic linkages. In some embodiments, provided oligonucleotides comprise one or more phosphoryl guanidine internucleotidic linkages. In some embodiments, a neutral internucleotidic linkage or non-negatively charged internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, each neutral internucleotidic linkage or non-negatively charged internucleotidic linkage is independently a phosphoryl guanidine internucleotidic linkage. In some embodiments, each neutral internucleotidic linkage and non-negatively charged internucleotidic linkage is independently n001.

[00895] In some embodiments, each internucleotidic linkage in a provided oligonucleotide is independently selected from a phosphorothioate internucleotidic linkage, a phosphoryl guanidine internucleotidic linkage, and a natural phosphate linkage. In some embodiments, each internucleotidic linkage in a provided oligonucleotide is independently selected from a phosphorothioate internucleotidic linkage, n001, and a natural phosphate linkage.

[00896] Various types of internucleotidic linkages may be utilized in combination of other structural elements, e.g., sugars, to achieve desired oligonucleotide properties and/or activities. For example, the present disclosure routinely utilizes modified internucleotidic linkages and modified sugars, optionally with natural phosphate linkages and natural sugars, in designed oligonucleotides. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more modified sugars. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more modified sugars and one or more modified internucleotidic linkages, one or more of which are natural phosphate linkages.

[00897] In some embodiments, an internucleotidic linkage is a phosphoryl guanidine, phosphoryl amidine, phosphoryl isourea, phosphoryl isothiourea, phosphoryl imidate, or phosphoryl imidothioate internucleotidic linkage, e.g., those as described in US 20170362270.

[00898] As appreciated by those skilled in the art, many other types of internucleotidic linkages may be utilized in accordance with the present disclosure, for example, those described in U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,177,195; 5,023,243; 5,034,506; 5,166,315; 5,185,444; 5,188,897; 5,214,134; 5,216,141; 5,235,033; 5,264,423; 5,264,564; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,938; 5,405,939; 5,434,257; 5,453,496; 5,455,233; 5,466,677; 5,466,677; 5,470,967; 5,476,925; 5,489,677; 5,519,126; 5,536,821; 5,541,307; 5,541,316; 5,550,111; 5,561,225; 5,563,253; 5,571,799; 5,587,361; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,625,050; 5,633,360; 5,64,562; 5,663,312; 5,677,437; 5,677,439; 6,160,109; 6,239,265; 6,028,188; 6,124,445; 6,169,170; 6,172,209; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715;

6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; or RE39464. In some embodiments, a modified internucleotidic linkage is one described in US 9982257, US 20170037399, US 20180216108, WO 2017192664, WO 2017015575, WO 2017062862, WO 2018067973, WO 2017160741, WO 2017192679, WO 2017210647, WO 2018098264, WO 2018223056, WO 2018237194, or WO 2019055951, the nucleobases, sugars, internucleotidic linkages, chiral auxiliaries/reagents, and technologies for oligonucleotide synthesis (reagents, conditions, cycles, etc.) of each of which is independently incorporated herein by reference. In some embodiments, an internucleotidic linkage is described in WO 2012/030683, WO 2021/030778, WO 2019112485, US 20170362270, WO 2018156056, WO 2018056871, WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376, and can be utilized in accordance with the present disclosure.

[00899] In some embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a non-negatively charged internucleotidic linkage (e.g., n001). In some embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a neutral internucleotidic linkage (e.g., n001).

[00900] In some embodiments, an oligonucleotide comprises one or more nucleotides that independently comprise a phosphorus modification prone to "autorelease" under certain conditions. That is, under certain conditions, a particular phosphorus modification is designed such that it self-cleaves from the oligonucleotide to provide, e.g., a natural phosphate linkage. In some embodiments, such a phosphorus modification has a structure of $-O-L-R^1$, wherein L is L^B as described herein, and R^1 is R' as described herein. In some embodiments, a phosphorus modification has a structure of $-S-L-R^1$, wherein each L and R^1 is independently as described in the present disclosure. Certain examples of such phosphorus modification groups can be found in US 9982257. In some embodiments, an autorelease group comprises a morpholino group. In some embodiments, an autorelease group is characterized by the ability to deliver an agent to the internucleotidic phosphorus linker, which agent facilitates further modification of the phosphorus atom such as, e.g., desulfurization. In some embodiments, the agent is water and the further modification is hydrolysis to form a natural phosphate linkage.

[00901] In some embodiments, an oligonucleotide comprises one or more internucleotidic linkages that improve one or more pharmaceutical properties and/or activities of the oligonucleotide. It is well documented in the art that certain oligonucleotides are rapidly degraded by nucleases and exhibit poor cellular uptake through the cytoplasmic cell membrane (Poijarvi-Virta et al., Curr. Med. Chem. (2006), 13(28);3441-65; Wagner et al., Med. Res. Rev. (2000), 20(6):417-51; Peyrottes et al., Mini Rev. Med. Chem. (2004), 4(4):395-408; Gosselin et al., (1996), 43(1):196-208; Bologna et al., (2002), Antisense & Nucleic Acid Drug Development 12:33-41). Vives et al. (Nucleic Acids Research (1999), 27(20):4071-76) reported that tert-butyl SATE pro-oligonucleotides displayed markedly increased cellular penetration compared to the parent oligonucleotide under certain conditions.

[00902] Oligonucleotides can comprise various number of natural phosphate linkages. In some embodiments, 5% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 10% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 15% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 20% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 25% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 30% or more of the internucleotidic linkages of [provided] oligonucleotides are natural phosphate linkages. In some embodiments, 35% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, 40% or more of the internucleotidic linkages of provided oligonucleotides are natural phosphate linkages. In some embodiments, provided oligonucleotides comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages. In some embodiments, provided oligonucleotides comprises 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages. In some embodiments, the number of natural phosphate linkages is 2. In some embodiments, the number of natural phosphate linkages is 3. In some embodiments, the number of natural phosphate linkages is 4. In some embodiments, the number of natural phosphate linkages is 5. In some embodiments, the number of natural phosphate linkages is 6. In some embodiments, the number of natural phosphate linkages is 7. In some embodiments, the number of natural phosphate linkages is 8. In some embodiments, some or all of the natural phosphate linkages are consecutive. In some embodiments, no more than a certain number of internucleotidic linkages of the provided oligonucleotides are natural phosphate linkages, e.g., no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, no more than 6, no more than 7, no more than 8, no more than 9, no more than 10, no more than 11, no more than 12, no more than 13, no more than 14, no more than 15, no more than 16, no more than 17, no more than 18, no more than 19, no more than 20, no more than 21, no more than 22, no more than 23, no more than 24, no more than 25, no more than 26, no more than 27, no more than 28, no more than 29, or no more than 30 natural phosphate linkages. In some embodiments, provided oligonucleotides comprise no natural phosphate linkages.

[00903] In some embodiments, the present disclosure demonstrates that, in at least some cases, *S*p internucleotidic linkages, among other things, at the 5'- and/or 3'-end can improve oligonucleotide stability. In some embodiments, the present disclosure demonstrates that, among other things, natural phosphate linkages and/or *R*p internucleotidic linkages may improve removal of oligonucleotides from a system. As appreciated by a person having ordinary skill in the art, various assays known in the art can be utilized to assess such properties in accordance with the present disclosure.

[00904] In some embodiments, each phosphorothioate internucleotidic linkage in an oligonucleotide or a portion thereof (e.g., a domain, a subdomain, etc.) is independently chirally controlled. In some embodiments, each is independently *S*p or *R*p. In some embodiments, a high level is *S*p as described herein. In some embodiments, each phosphorothioate internucleotidic linkage in an oligonucleotide or a portion thereof is

chirally controlled and is *S*p. In some embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

[00905] In some embodiments, as illustrated in certain examples, an oligonucleotide or a portion thereof comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, the number of non-negatively charged internucleotidic linkages in an oligonucleotide or a portion thereof is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, it is about 1. In some embodiments, it is about 2. In some embodiments, it is about 3. In some embodiments, it is about 4. In some embodiments, it is about 5. In some embodiments, it is about 6. In some embodiments, it is about 7. In some embodiments, it is about 8. In some embodiments, it is about 9. In some embodiments, it is about 10. In some embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In some embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In some embodiments, all non-negatively charged internucleotidic linkages in an oligonucleotide or a portion thereof are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In some embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of an oligonucleotide or a portion thereof. In some embodiments, the last two or three or four internucleotidic linkages of an oligonucleotide or a portion thereof comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In some embodiments, the last two or three or four internucleotidic linkages of an oligonucleotide or a portion thereof comprise at least one internucleotidic linkage that is not n001. In some embodiments, the internucleotidic linkage linking the first two nucleosides of an oligonucleotide or a portion thereof is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the last two nucleosides of an oligonucleotide or a portion thereof is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage linking the first two nucleosides of an oligonucleotide or a portion thereof is a phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p. In some embodiments, the internucleotidic linkage linking the last two nucleosides of an oligonucleotide or a portion thereof is a phosphorothioate internucleotidic linkage. In some embodiments, it is *S*p.

[00906] In some embodiments, one or more chiral internucleotidic linkages are chirally controlled and one or more chiral internucleotidic linkages are not chirally controlled. In some embodiments, each phosphorothioate

internucleotidic linkage is independently chirally controlled, and one or more non-negatively charged internucleotidic linkage are not chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled, and each non-negatively charged internucleotidic linkage is not chirally controlled. In some embodiments, the internucleotidic linkage between the first two nucleosides of an oligonucleotide is a non-negatively charged internucleotidic linkage. In some embodiments, the internucleotidic linkage between the last two nucleosides are each independently a non-negatively charged internucleotidic linkage. In some embodiments, both are independently non-negatively charged internucleotidic linkages. In some embodiments, an oligonucleotide comprises one or more additional internucleotidic linkages, e.g., one of which is between the nucleosides at positions -1 and -2 relative to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) (the two nucleosides immediately 3' to a nucleoside opposite to a target nucleoside (e.g., in …$N_0N_{-1}N_{-2}$…., N_0 is a nucleoside opposite to a target nucleoside, N_{-1} and N_{-2} are at positions -1 and -2, respectively). In some embodiments, each non-negatively charged internucleotidic linkage is independently neutral internucleotidic linkage. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001.

[00907] As demonstrated herein, in some embodiments, non-negatively charged internucleotidic linkages such as n001 may provide improved properties and/or activities. In some embodiments, in an oligonucleotide a 5'-end internucleotidic linkage and/or a 3'-end internucleotidic linkage, each of which is independently bonded to two nucleosides comprising a nucleobase as described herein, is a non-negatively charged internucleotidic linkage as described herein. In some embodiments, the first one or more (e.g., the first 1, 2, and/or 3), and/or the last one or more (e.g., the last 1, 2, 3, 4, 5, 6 or 7) internucleotidic linkages, each of which is independently bonded to two nucleosides in a first domain, is independently a non-negatively charged internucleotidic linkage. In some embodiments, the first internucleotidic linkage of a first domain is a non-negatively charged internucleotidic linkage. In some embodiments, the last internucleotidic linkage that bonds to two nucleosides of a first domain is a non-negatively charged internucleotidic linkage. In some embodiments, the last internucleotidic linkage of a second domain is a non-negatively charged internucleotidic linkage. In some embodiments, one or more of internucleotidic linkages in the middle of a second domain, e.g., one or more of the 4th, 5th and 6th internucleotidic linkages, each of which independently bonds to two nucleosides of a second domain, is independently a non-negatively charged internucleotidic linkage. In some embodiments, the 11th internucleotidic linkage that bonds to two nucleosides of a second domain is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage that is not bonded to a nucleoside opposite to a target nucleoside but is bonded to its 3' immediate nucleoside is a non-negatively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, each non-negatively charged internucleotidic linkage is n001. In some embodiments, a non-negatively charged internucleotidic linkage is stereorandom. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In some embodiments, a non-negatively

charged internucleotidic linkage is chirally controlled and is *S*p. In some embodiments, each non-negatively charged internucleotidic linkage is independently chirally controlled. In some embodiments, one or more internucleotidic linkages of a first domain, e.g., one or more of the 4th, 5th, 6th, 7th and 8th internucleotidic linkages each of which is independently bonded to two nucleosides of a first domain, is independently not a non-negatively charged internucleotidic linkage. In some embodiments, one or more internucleotidic linkages of a second domain, e.g., one or more of the 1st, 2nd, 3rd, 7th, 8th, 9th, 12th and 13th internucleotidic linkages each of which is independently bonded to two nucleosides of a first domain, is independently not a non-negatively charged internucleotidic linkage. In some embodiments, one or both of the 2nd and the 3rd internucleotidic linkages of a second domain is not a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage that is not a non-negatively charged internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, it is a stereorandom phosphorothioate internucleotidic linkage. In some embodiments, it is a *R*p chirally controlled phosphorothioate internucleotidic linkage. In some embodiments, it is a *S*p chirally controlled phosphorothioate internucleotidic linkage.

[00908] In some embodiments, one or more or all internucleotidic linkages at positions +11, +9, +5, -2, and -5 of a nucleoside opposite to a target adenosine are independently non-negatively charged internucleotidic linkages ("+" is counting from a nucleoside opposite to a target adenosine toward the 5'-end of an oligonucleotide with the internucleotidic linkage at the +1 position being the internucleotidic linkage between a nucleoside opposite to a target adenosine and its 5' side neighboring nucleoside (e.g., being between N_1 and N_0 of 5'-$N_1N_0N_{-1}$-3', wherein as described herein N_0 is a nucleoside opposite to a target adenosine), and "-" is counting from the nucleoside toward the 3'-end of an oligonucleotide with the internucleotidic linkage at the -1 position being the internucleotidic linkage between a nucleoside opposite to a target adenosine and its 3' side neighboring nucleoside (e.g., being between N_{-1} and N_0 of 5'-$N_1N_0N_{-1}$-3', wherein as described herein N_0 is the nucleoside opposite to a target adenosine)). In some embodiments, the first internucleotidic linkage of an oligonucleotide is a non-negatively charged internucleotidic linkage. In some embodiments, the last internucleotidic linkage of an oligonucleotide is a non-negatively charged internucleotidic linkage. In some embodiments, the first and last internucleotidic linkages of an oligonucleotide are each independently a non-negatively charged internucleotidic linkage. In some embodiments, one or more or all internucleotidic linkages at positions +21, +20, +18, +17, +16, +15, +14, +13, +12, +11, +10, +6, +5, +4, and -2 are independently non-negatively charged internucleotidic linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, one or more or all internucleotidic linkages at positions +24, +23, +22, +19, +16, +15, +14, +13, +12, +11, +10, +6, +5, +4, -2, and -5 are independently non-negatively charged internucleotidic linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, one or more or all internucleotidic linkages at positions +23, +22, +19, +16, +15, +14, +13, +12, +11, +10, +6, +5, +4, and -2 are independently non-negatively charged internucleotidic linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, the first and last internucleotidic linkages of an oligonucleotide are independently non-negatively charged internucleotidic

linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, the first and the last internucleotidic linkages and one or more or all internucleotidic linkages at positions +23, +22, +19, +16, +15, +14, +13, +12, +11, +10, +6, +5, +4, and -2 are independently non-negatively charged internucleotidic linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, the first and the last internucleotidic linkages are both *R*p. In some embodiments, each phosphorothioate internucleotidic linkages are *S*p. In some embodiments, an internucleotidic linkage at position -2 is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -5 is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +5 is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +9 is a non-negatively charged internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +11 is a non-negatively charged internucleotidic linkage. In some embodiments, each of the internucleotidic linkages at positions -2, and -5 is independently a non-negatively charged internucleotidic linkage. In some embodiments, each of the internucleotidic linkages at positions +5, -2, and -5 is independently a non-negatively charged internucleotidic linkage. In some embodiments, each of the internucleotidic linkages at positions +11, +9, -2, and -5 is independently a non-negatively charged internucleotidic linkage. In some embodiments, each of the internucleotidic linkages at positions +11, +9, +5, -2, and -5 is independently a non-negatively charged internucleotidic linkage. In some embodiments, one or more or each of the 1st, 14th, 16th, 20th, 26th, and 29th internucleotidic linkages (unless otherwise specified, from the 5'-end) is independently a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises no non-negatively charged internucleotidic linkages to the 5' side of a nucleoside opposite to a target adenosine except that the first internucleotidic linkage of an oligonucleotide may be optionally a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises no internal non-negatively charged internucleotidic linkages except at position -2. In some embodiments, one or both of the first and last internucleotidic linkages of a first domain is independently a non-negatively charged internucleotidic linkage. In some embodiments, one or both of the first and last internucleotidic linkages of a second domain is independently a non-negatively charged internucleotidic linkage. In some embodiments, one or both of the first and last internucleotidic linkages of an oligonucleotide is independently a non-negatively charged internucleotidic linkage. In some embodiments, both of the first and last internucleotidic linkages of a first domain are independently non-negatively charged internucleotidic linkages. In some embodiments, both of the first and last internucleotidic linkages of a second domain are independently non-negatively charged internucleotidic linkages. In some embodiments, both of the first and last internucleotidic linkages of an oligonucleotide are independently non-negatively charged internucleotidic linkages. In some embodiments, each non-negatively charged internucleotidic linkage is independently a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, each non-negatively charged internucleotidic linkage is independently a phosphoryl guanidine internucleotidic linkage.

In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, each non-negatively charged internucleotidic linkage is independently *R*p, *S*p, or non-chirally controlled. In some embodiments, one or more non-negatively charged internucleotidic linkages are independently not chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently not chirally controlled. In some embodiments, one or more non-negatively charged internucleotidic linkages are independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is *R*p. In some embodiments, each non-negatively charged internucleotidic linkage is *S*p. In some embodiments, an internucleotidic linkage, e.g., n001, bonded to an inosine or deoxyinosine or 2'-modified inosine (e.g., 2'-OH replaced with a non-H moiety such as −F, −OMe, −MOE, etc.) at its 3' position is non-chirally controlled or is chirally controlled and *S*p. In some embodiments, it is chirally controlled and *S*p. In some embodiments, oligonucleotides and compositions thereof comprising chirally controlled *S*p non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) bonded to 3'-positions of nucleosides comprising hypoxanthine provide various advantages over corresponding stereorandom or *R*p internucleotidic linkages, e.g., the same or better properties and/or activities, improved manufacturing efficiency, and/or lowered manufacturing cost, etc. In some embodiments, it was observed that processes for constructing chirally controlled *S*p non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) bonded to 3'-positions of nucleosides comprising hypoxanthine can be performed more readily (e.g., higher reagent concentrations, smaller solution volumes, shorter reaction times, etc.) and/or with lower cost (e.g., more easily accessible materials).. In some embodiments, oligonucleotides and compositions thereof comprising chirally controlled *R*p phosphorothioate internucleotidic linkages bonded to 3'-positions of nucleosides comprising hypoxanthine provide various advantages over corresponding stereorandom or *S*p internucleotidic linkages, e.g., the same or better properties and/or activities, improved manufacturing efficiency, and/or lowered manufacturing cost, etc. In some embodiments, processes for constructing chirally controlled *R*p phosphorothioate internucleotidic linkages bonded to 3'-positions of nucleosides comprising hypoxanthine can be performed more readily (e.g., higher reagent concentrations, smaller solution volumes, shorter reaction times, etc.) and/or with lower cost (e.g., more easily accessible materials).

[00909] In some embodiments, an oligonucleotide comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, etc.) natural phosphate linkages. In some embodiments, both nucleosides bonded to a natural phosphate linkage are independently a 2'-modified sugar. In some embodiments, both nucleosides bonded to a majority (e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) of natural phosphate linkages are independently a 2'-modified sugar. In some embodiments, both nucleosides bonded to each natural phosphate linkage are independently a 2'-modified sugar. In some embodiments, a 2'-modified sugar is a bicyclic sugar or 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some

embodiments, each 2'-modified sugar is independently a bicyclic sugar or 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-modified sugar is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-modified sugar is independently a 2'-OMe modified sugar or a 2'-MOE modified sugar. In some embodiments, each 2'-modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-modified sugar is independently a 2'-MOE modified sugar. In some embodiments, a natural phosphate linkage is utilized with a non-negatively charged internucleotidic linkage (e.g., a phosphoryl guanidine internucleotidic linkage such as n001). In some embodiments, an oligonucleotide comprises alternating natural phosphate linkages and non-negatively charged internucleotidic linkages (e.g., a phosphoryl guanidine internucleotidic linkage such as n001) (e.g., see WV-43047).

[00910] In some embodiments, one or more internucleotidic linkages at positions -1 and -2 are independently *R*p phosphorothioate internucleotidic linkages. In some embodiments, one or more internucleotidic linkages at positions -3, -2, -1, +1, +3, +4, +5, +7, +8, +9, +10, +11, +12, +13,+16, +17 and +18 are independently *R*p phosphorothioate internucleotidic linkages. In some embodiments, an internucleotidic linkage at position -3 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -2 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -1 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +1 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +3 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +4 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +5 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +7 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +8 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +9 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +10 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +11 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +12 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +13 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +16 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +17 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +18 is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an oligonucleotide contains one and only one *R*p phosphorothioate internucleotidic linkage. In some embodiments, it contains two and no more than two. In some embodiments, it contains three and no more than three. In some embodiments, it contains four and no more than four. In some embodiments, it contains five and no more than

five.

[00911] In some embodiments, a non-negatively charged internucleotidic linkage bonded to 3'-carbon of dI is *S*p. In some embodiments, a non-negatively charged internucleotidic linkage bonded to 3'-carbon of dI is *S*p. In some embodiments, a phosphoryl guanidine internucleotidic linkage bonded to 3'-carbon of dI is *S*p. In some embodiments, a n001 internucleotidic linkage bonded to 3'-carbon of dI is *S*p. In some embodiments, each non-negatively charged internucleotidic linkage bonded to 3'-carbon of dI is independently *S*p. In some embodiments, each neutral internucleotidic linkage bonded to 3'-carbon of dI is independently *S*p. In some embodiments, each phosphoryl guanidine internucleotidic linkage bonded to 3'-carbon of dI is independently *S*p. In some embodiments, each n001 bonded to 3'-carbon of dI is independently *S*p.

[00912] In some embodiments, a controlled level of oligonucleotides in a composition are desired oligonucleotides. In some embodiments, of all oligonucleotides in a composition that share a common base sequence (e.g., a desired sequence for a purpose), or of all oligonucleotides in a composition, level of desired oligonucleotides (which may exist in various forms (e.g., salt forms) and typically differ only at non-chirally controlled internucleotidic linkages (various forms of the same stereoisomer can be considered the same for this purpose)) is about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%. In some embodiments, a level is at least about 50%. In some embodiments, a level is at least about 60%. In some embodiments, a level is at least about 70%. In some embodiments, a level is at least about 75%. In some embodiments, a level is at least about 80%. In some embodiments, a level is at least about 85%. In some embodiments, a level is at least about 90%. In some embodiments, a level is or is at least $(DS)^{nc}$, wherein DS is about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% and nc is the number of chirally controlled internucleotidic linkages as described in the present disclosure (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more). In some embodiments, a level is or is at least $(DS)^{nc}$, wherein DS is 95%-100%.

[00913] Various types of internucleotidic linkages may be utilized in combination of other structural elements, e.g., sugars, to achieve desired oligonucleotide properties and/or activities. For example, the present disclosure routinely utilizes modified internucleotidic linkages and modified sugars, optionally with natural phosphate linkages and natural sugars, in designing oligonucleotides. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more modified sugars. In some embodiments, the present disclosure provides an oligonucleotide comprising one or more modified sugars and one or more modified internucleotidic linkages, one or more of which are natural phosphate linkages.

[00914] In some embodiments, provided oligonucleotides comprise a number of natural RNA sugars (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, two or more or all of them are optionally consecutive). In some embodiments, such oligonucleotides comprise

modified sugars, e.g., 2' modified sugars (e.g., 2'-F, etc.) and/or 2'-OR modified sugars wherein R is not –H (e.g., 2-OMe, 2-MOE, etc.) at one or both ends, and/or various modified internucleotidic linkages (e.g., phosphorothioate internucleotidic linkages, non-negatively charged internucleotidic linkages, etc.). In some embodiments, at the 5'-end there are one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 more such 2'-OR modified sugars, wherein R is not –H. In some embodiments, at the 3'-end there are one or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 more such 2'-OR modified sugars, wherein R is not –H. In some embodiments, each 2'-modified sugar is independently a 2'-OR modified sugar wherein R is not –H. In some embodiments, as described herein, 2'-OR is 2'-OMe. In some embodiments, 2'-OR is 2'-MOE. In some embodiments, each of 2'-OR is independently 2'-OMe or 2'-MOE. In some embodiments, each 2'-OR is 2'-OMe.

[00915] In some embodiments, stability of various internucleotidic linkages is assessed. In some embodiments, internucleotidic linkages are exposed to various conditions utilized for oligonucleotide manufacturing, e.g., solid phase oligonucleotide synthesis, including reagents, solvents, temperatures (in some cases, temperatures higher than room temperature), cleavage conditions, deprotection conditions, purification conditions, etc., and stability is assessed. In some embodiments, stable internucleotidic linkages (e.g., those having no more than than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% degradation when exposed to one or more conditions and/or processes, or after a complete oligonucleotide manufacturing process) are selected for utilization in various oligonucleotide compositions and applications.

Additional Chemical Moieties

[00916] In some embodiments, an oligonucleotide comprises one or more additional chemical moieties. Various additional chemical moieties, e.g., targeting moieties, carbohydrate moieties, lipid moieties, etc. are known in the art and can be utilized in accordance with the present disclosure to modulate properties and/or activities of provided oligonucleotides, e.g., stability, half life, activities, delivery, pharmacodynamics properties, pharmacokinetic properties, etc. In some embodiments, certain additional chemical moieties facilitate delivery of oligonucleotides to desired cells, tissues and/or organs, including but not limited the cells of the central nervous system. In some embodiments, certain additional chemical moieties facilitate internalization of oligonucleotides. In some embodiments, certain additional chemical moieties increase oligonucleotide stability. In some embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into oligonucleotides.

[00917] In some embodiments, an additional chemical moiety is or comprises a small molecule moiety. In some embodiments, a small molecule is a ligand of a protein (e.g., receptor). In some embodiments, a small molecule binds to a polypeptide. In some embodiments, a small molecule is an inhibitor of a polypeptide. In some embodiments, an additional chemical moiety is or comprises a peptide moiety (e.g., an antibody). In some embodiments, an additional chemical moiety is or comprises a nucleic acid moiety. In some embodiments, a nucleic acid provides a new property and/or activity. In some embodiments, a nucleic acid moiety forms a duplex or other secondary structure with the original oligonucleotide chain (before conjugation)

or a portion thereof. In some embodiments, a nucleic acid is or comprises an oligonucleotide targeting the same or a different target, and may perform its activity through the same or a different mechanism. In some embodiments, a nucleic acid is or comprises a RNAi agent. In some embodiments, a nucleic acid is or comprises a miRNA agent. In some embodiments, a nucleic acid is or comprises RNase H dependent. In some embodiments, a nucleic acid is or comprises a gRNA. In some embodiments, a nucleic acid is or comprises an aptamer. In some embodiments, an additional chemical moiety is or comprises a carbohydrate moiety as described herein. Many useful agents, e.g., small molecules, peptides, carbohydrates, nucleic acid agents, etc., may be conjugated with oligonucleotides herein in accordance with the present disclosure.

[00918] In some embodiments, an oligonucleotide comprises an additional chemical moiety demonstrates increased delivery to and/or activity in an tissue compared to a reference oligonucleotide, e.g., a reference oligonucleotide which does not have the additional chemical moiety but is otherwise identical.

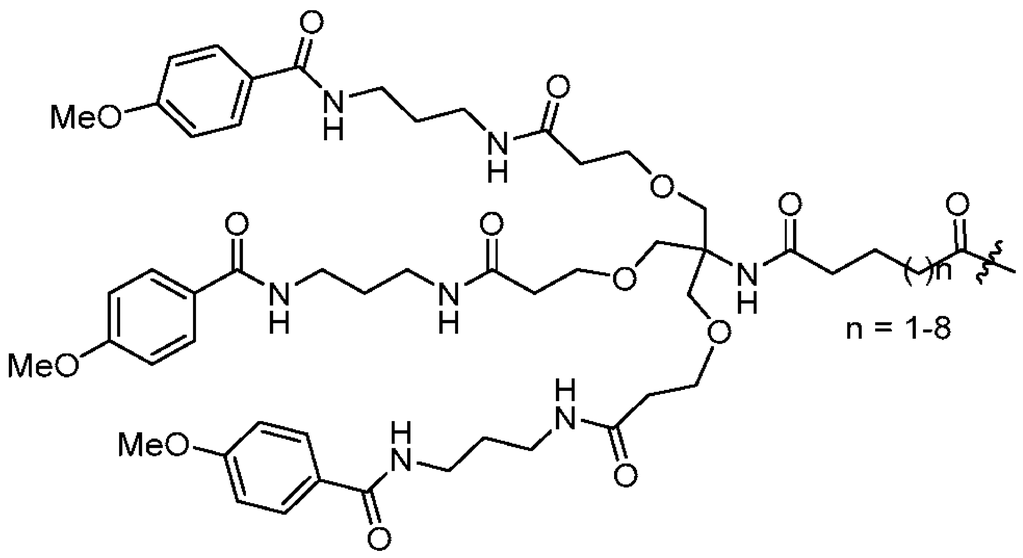
[00919] In some embodiments, non-limiting examples of additional chemical moieties include carbohydrate moieties, targeting moieties, etc., which, when incorporated into oligonucleotides, can improve one or more properties. In some embodiments, an additional chemical moiety is selected from: glucose, GluNAc (N-acetyl amine glucosamine) and anisamide moieties. In some embodiments, a provided oligonucleotide can comprise two or more additional chemical moieties, wherein the additional chemical moieties are identical or non-identical, or are of the same category (e.g., carbohydrate moiety, sugar moiety, targeting moiety, etc.) or not of the same category.

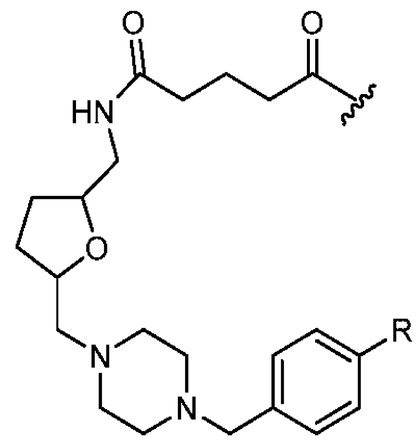
[00920] In some embodiments, an additional chemical moiety is a targeting moiety. In some embodiments, an additional chemical moiety is or comprises a carbohydrate moiety. In some embodiments, an additional chemical moiety is or comprises a lipid moiety. In some embodiments, an additional chemical moiety is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In some embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In some embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein receptor. In some embodiments, an additional chemical moiety facilitates delivery to liver.

[00921] In some embodiments, a provided oligonucleotide can comprise one or more linkers and additional chemical moieties (e.g., targeting moieties), and/or can be chirally controlled or not chirally controlled, and/or have a bases sequence and/or one or more modifications and/or formats as described herein.

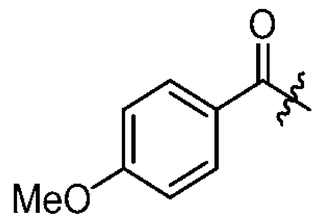
[00922] Various linkers, carbohydrate moieties and targeting moieties, including many known in the art, can be utilized in accordance with the present disclosure. In some embodiments, a carbohydrate moiety is a targeting moiety. In some embodiments, a targeting moiety is a carbohydrate moiety.

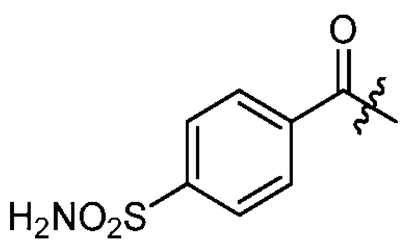
[00923] In some embodiments, a provided oligonucleotide comprises an additional chemical moiety suitable for delivery, e.g., glucose, GluNAc (N-acetyl amine glucosamine), anisamide, or a structure selected from:

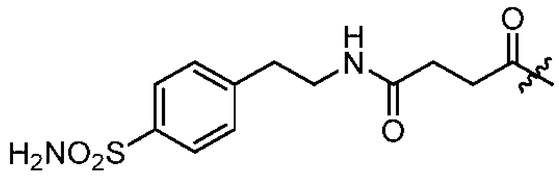


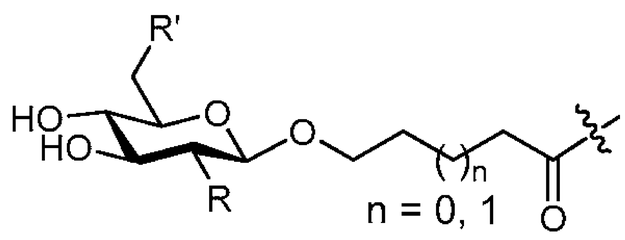


R = F, OMe, OH, NHAc, $NHCOCF_3$

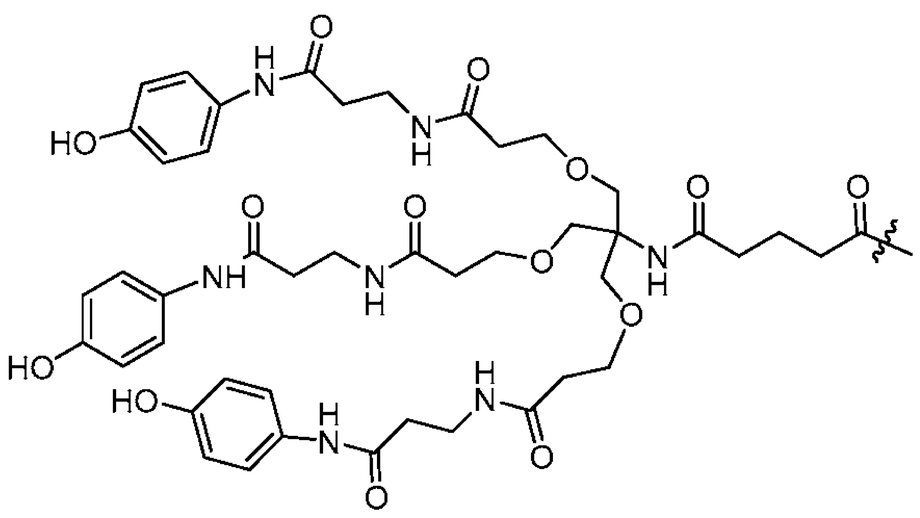


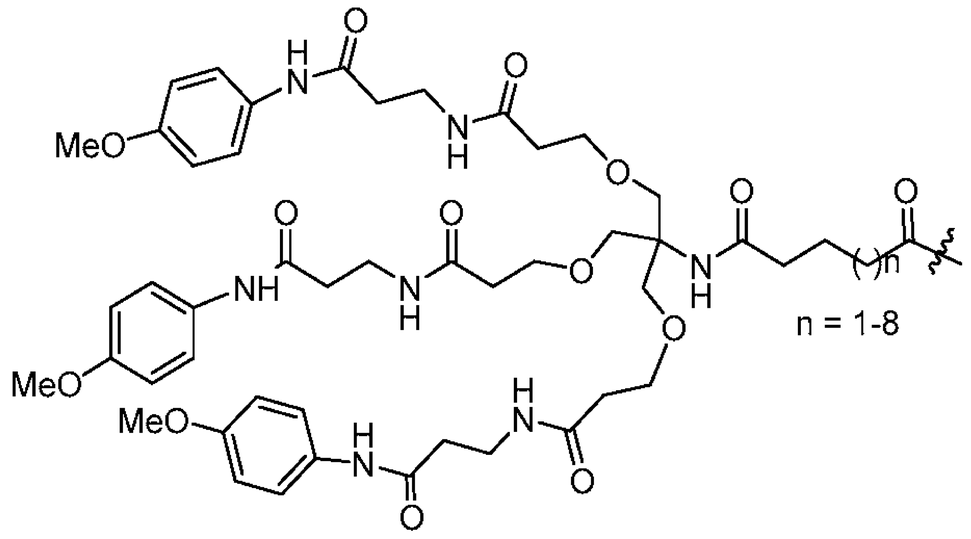


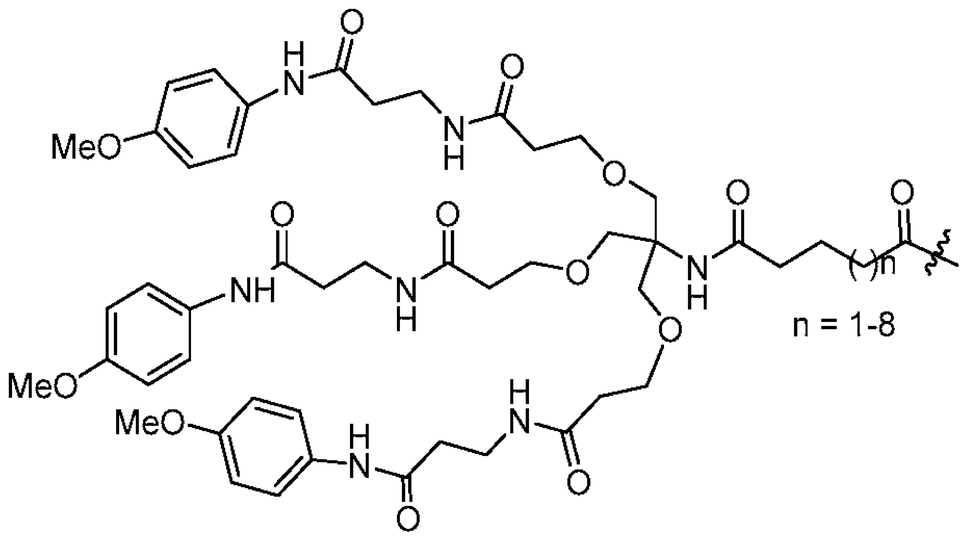


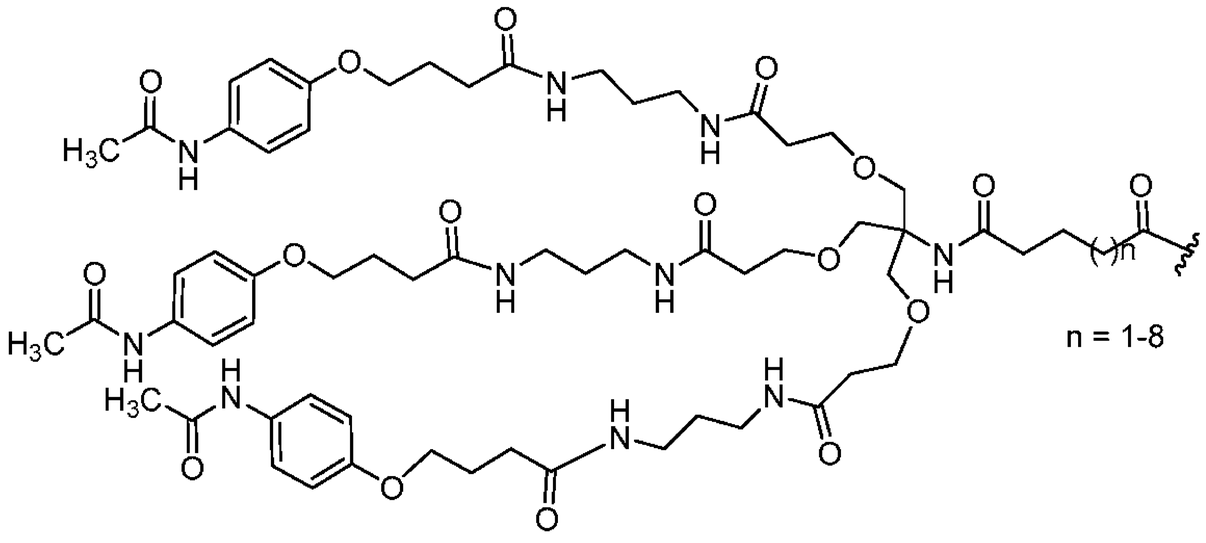


R = NHAc, R' = OH; R = NHCOC6H4OMe(p-anisoyl), R'=OH;
R = NHAc, R' = NHCOC6H4OMe(p-anisoyl);
R = OH, R' = NHCOC6H4OMe(p-anisoyl)









and

. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is

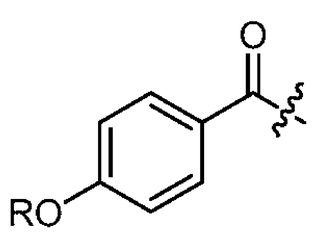
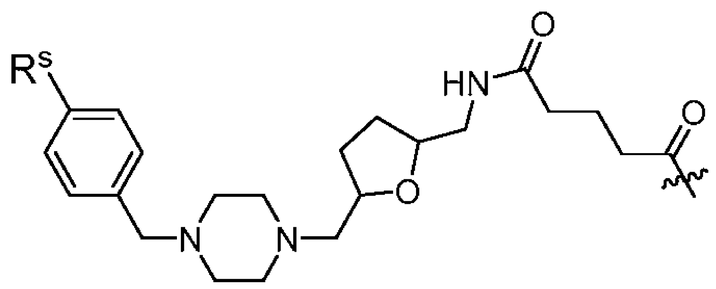
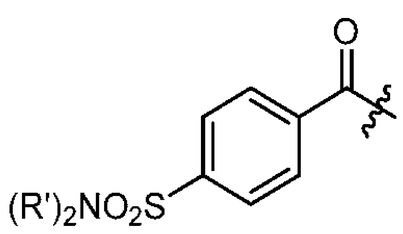
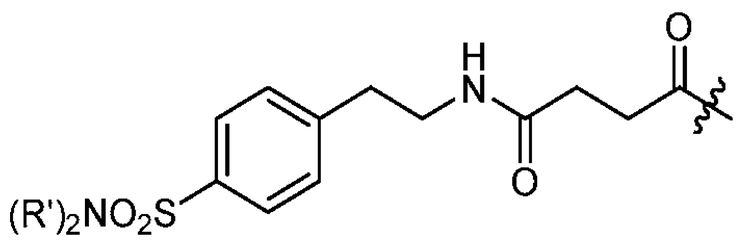
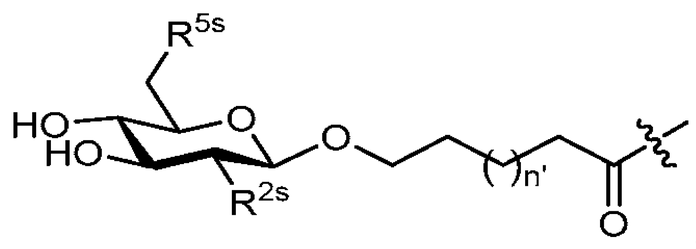
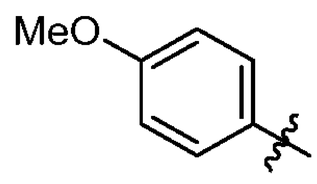
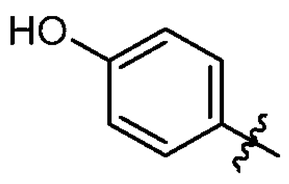
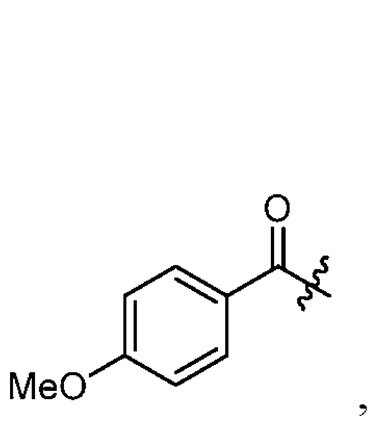
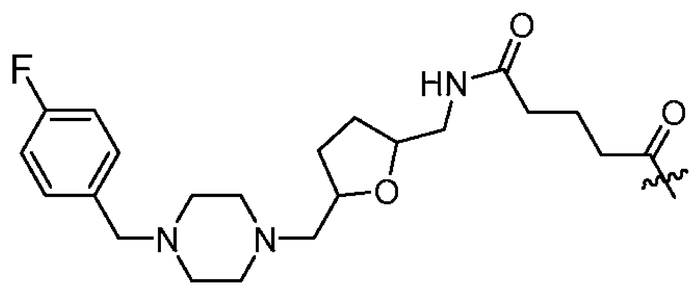
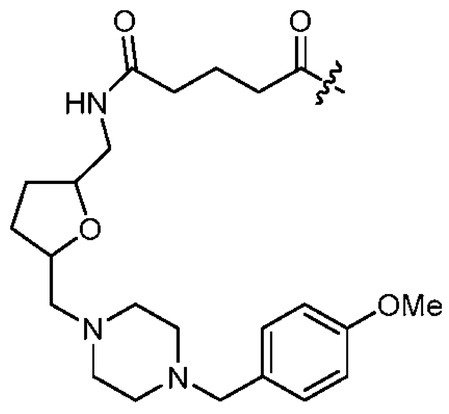
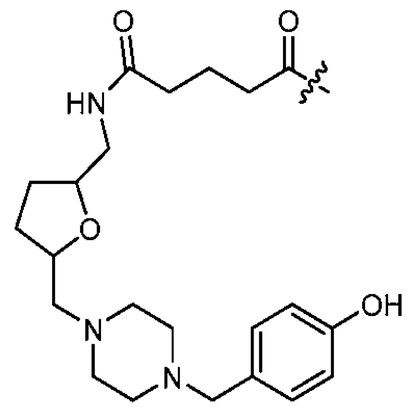
5. In some embodiments, n is 6. In some embodiments, n is 7. In some embodiments, n is 8.

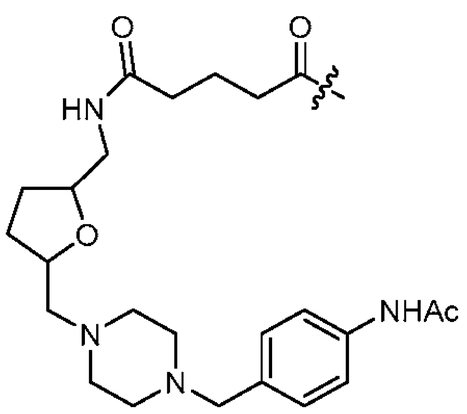
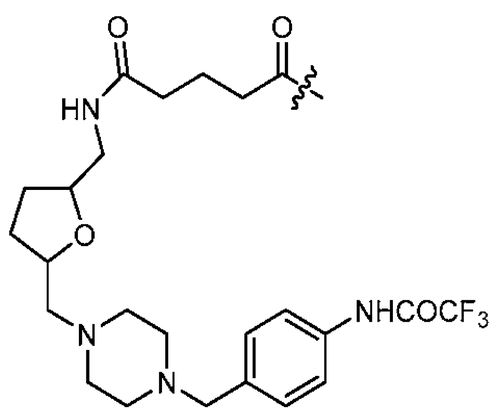
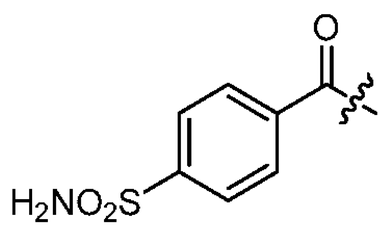
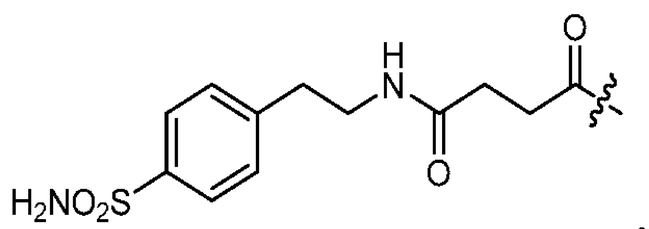
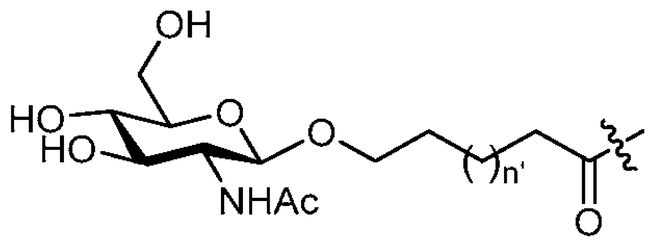
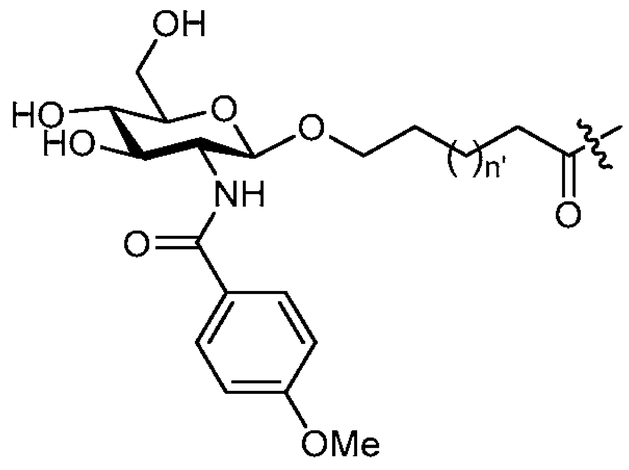
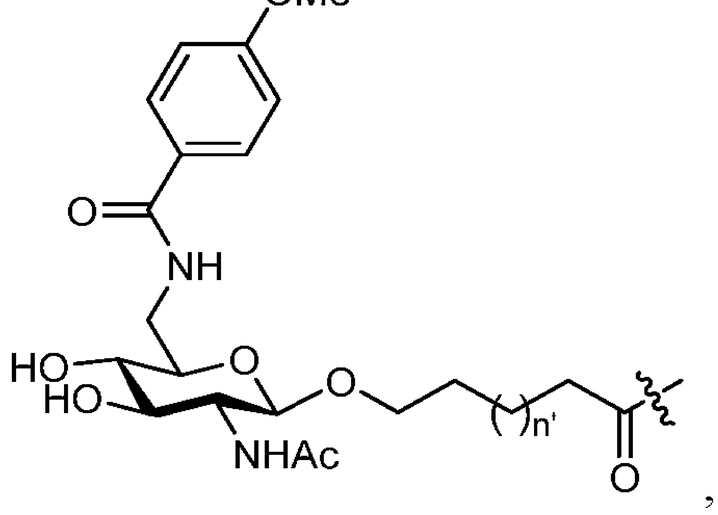
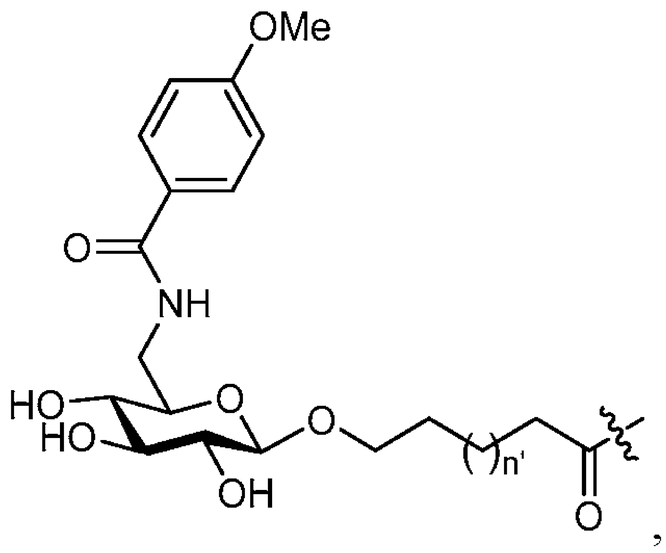
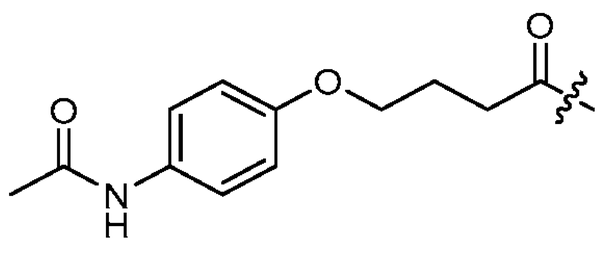
[00924] In some embodiments, additional chemical moieties are any of ones described in the Examples, including examples of various additional chemical moieties incorporated into various oligonucleotides.

[00925] In some embodiments, an additional chemical moiety conjugated to an oligonucleotide is capable of targeting the oligonucleotide to a cell in the central nervous system.

[00926] In some embodiments, an additional chemical moiety comprises or is a cell receptor ligand. In some embodiments, an additional chemical moiety comprises or is a protein binder, e.g., one binds to a cell surface protein. Such moieties among other things can be useful for targeted delivery of oligonucleotides to cells expressing the corresponding receptors or proteins. In some embodiments, an additional chemical moiety of a provided oligonucleotide comprises anisamide or a derivative or an analog thereof and is capable of targeting the oligonucleotide to a cell expressing a particular receptor, such as the sigma 1 receptor.

[00927] In some embodiments, a provided oligonucleotide is formulated for administration to a body cell and/or tissue expressing its target. In some embodiments, an additional chemical moiety conjugated to an oligonucleotide is capable of targeting the oligonucleotide to a cell.

[00928] In some embodiments, an additional chemical moiety is selected from optionally substituted phenyl,  ,  ,  ,  , and  , wherein n' is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and each other variable is as described in the present disclosure. In some embodiments, R^s is F. In some embodiments, R^s is OMe. In some embodiments, R^s is OH. In some embodiments, R^s is NHAc. In some embodiments, R^s is $NHCOCF_3$. In some embodiments, R' is H. In some embodiments, R is H. In some embodiments, R^{2s} is NHAc, and R^{5s} is OH. In some embodiments, R^{2s} is p-anisoyl, and R^{5s} is OH. In some embodiments, R^{2s} is NHAc and R^{5s} is p-anisoyl. In some embodiments, R^{2s} is OH, and R^{5s} is p-anisoyl. In some embodiments, an additional chemical moiety is selected from  ,  ,  ,  ,  ,  ,

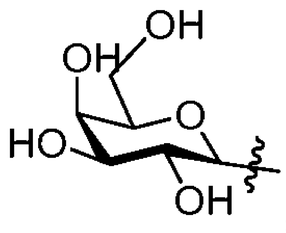
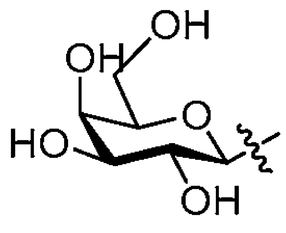
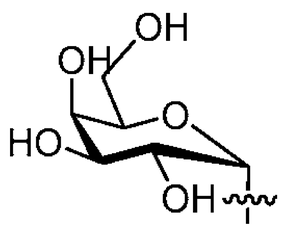
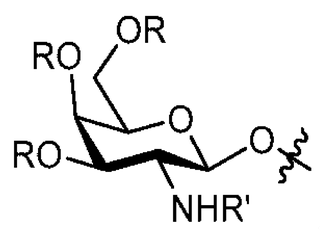
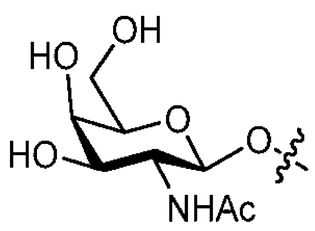
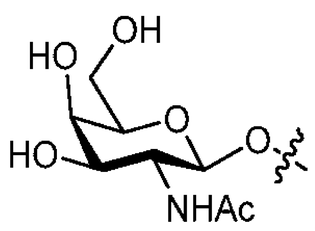
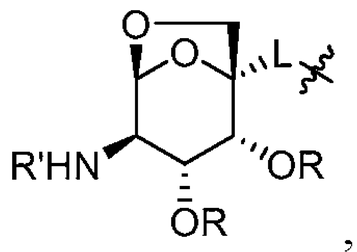
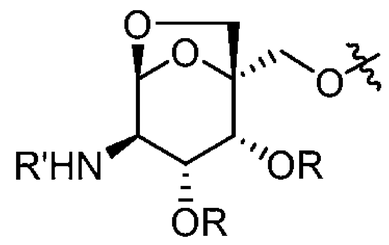
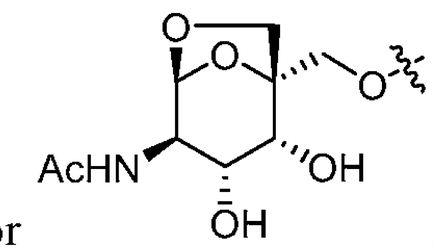










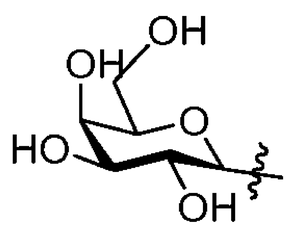
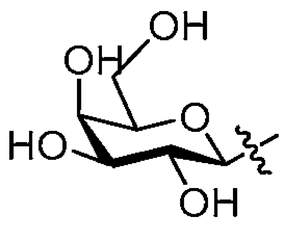
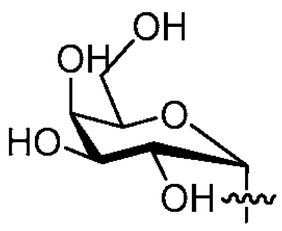
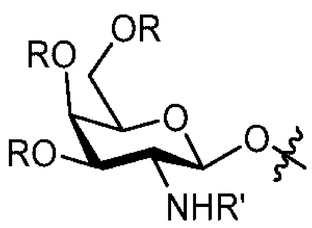
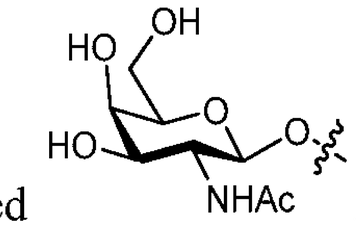
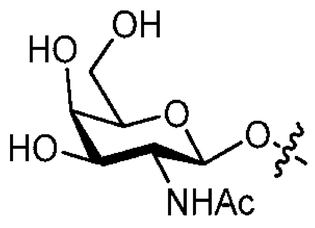
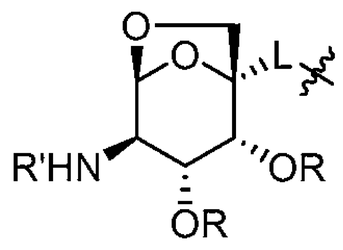
. In some embodiments, n' is 1. In some embodiments, n' is 0. In some embodiments, n" is 1. In some embodiments, n" is 2.

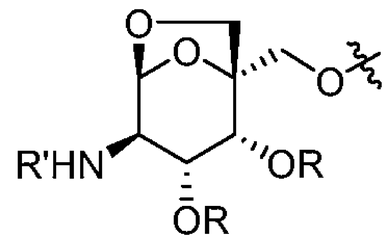
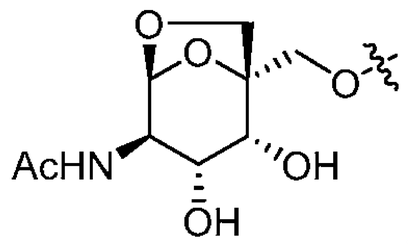
[00929] In some embodiments, an additional chemical moiety is or comprises an asialoglycoprotein receptor (ASGPR) ligand.

[00930] Without wishing to be bound by any particular theory, the present disclosure notes that ASGPR1 has also been reported to be expressed in the hippocampus region and/or cerebellum Purkinje cell layer of the mouse. http://mouse.brain-map.org/experiment/show/2048

[00931] Various other ASGPR ligands are known in the art and can be utilized in accordance with the present disclosure. In some embodiments, an ASGPR ligand is a carbohydrate. In some embodiments, an ASGPR ligand is GalNac or a derivative or an analog thereof. In some embodiments, an ASGPR ligand is one described in Sanhueza et al. J. Am. Chem. Soc., 2017, 139 (9), pp 3528–3536. In some embodiments, an ASGPR ligand is one described in Mamidyala et al. J. Am. Chem. Soc., 2012, 134, pp 1978−1981. In some embodiments, an ASGPR ligand is one described in US 20160207953. In some embodiments, an ASGPR ligand is a substituted-6,8-dioxabicyclo[3.2.1]octane-2,3-diol derivative disclosed in, e.g., US 20160207953. In some embodiments, an ASGPR ligand is one described in, e.g., US 20150329555. In some embodiments, an ASGPR ligand is a substituted-6,8-dioxabicyclo[3.2.1]octane-2,3-diol derivative disclosed e.g., in US 20150329555. In some embodiments, an ASGPR ligand is one described in US 8877917, US 20160376585,

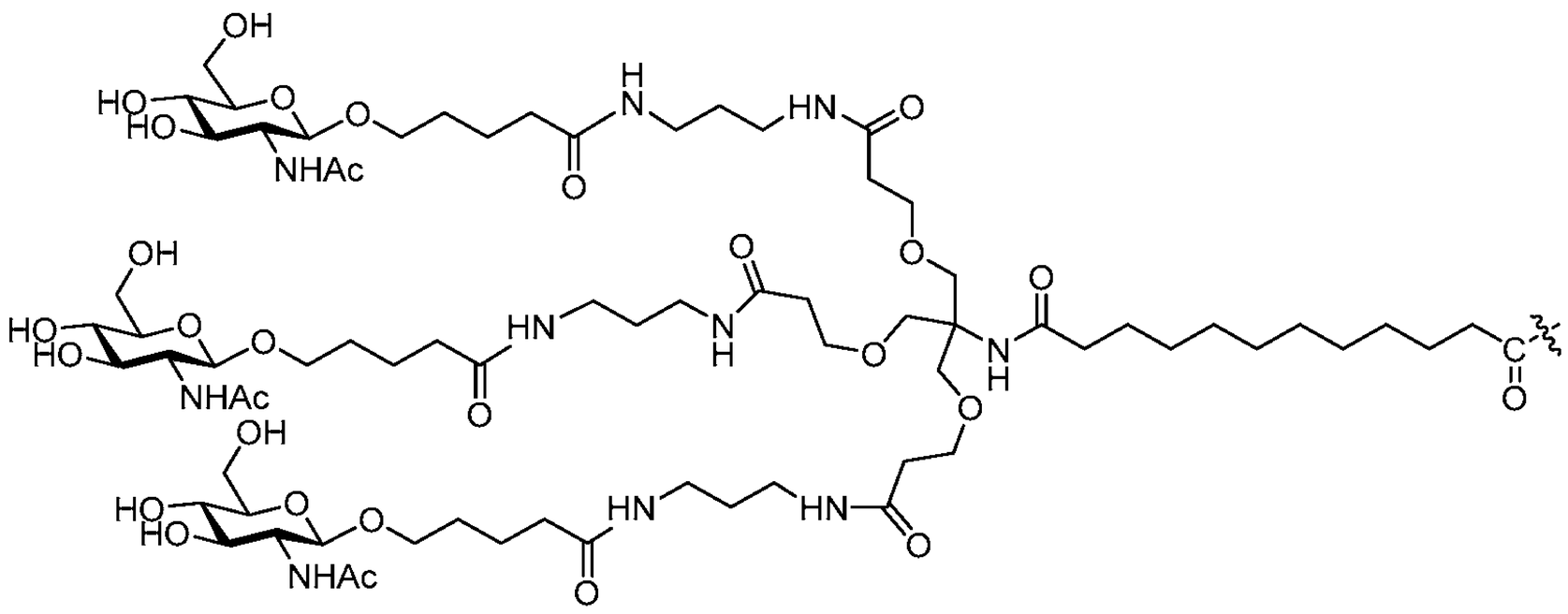
US 10086081, or US 8106022. ASGPR ligands described in these documents are incorporated herein by reference. Those skilled in the art will appreciate that various technologies are known in the art, including those described in these documents, for assessing binding of a chemical moiety to ASGPR and can be utilized in accordance with the present disclosure. In some embodiments, a provided oligonucleotide is conjugated to an ASGPR ligand. In some embodiments, a provided oligonucleotide comprises an ASGPR ligand. In some embodiments, an additional chemical moiety comprises an ASGPR ligand is  ,  ,  ,  ,  ,  ,  ,  ,  or , wherein each variable is independently as described in the present disclosure. In some embodiments, R is −H. In some embodiments, R' is −C(O)R.

[00932] In some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises optionally substituted  . In some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises  . In

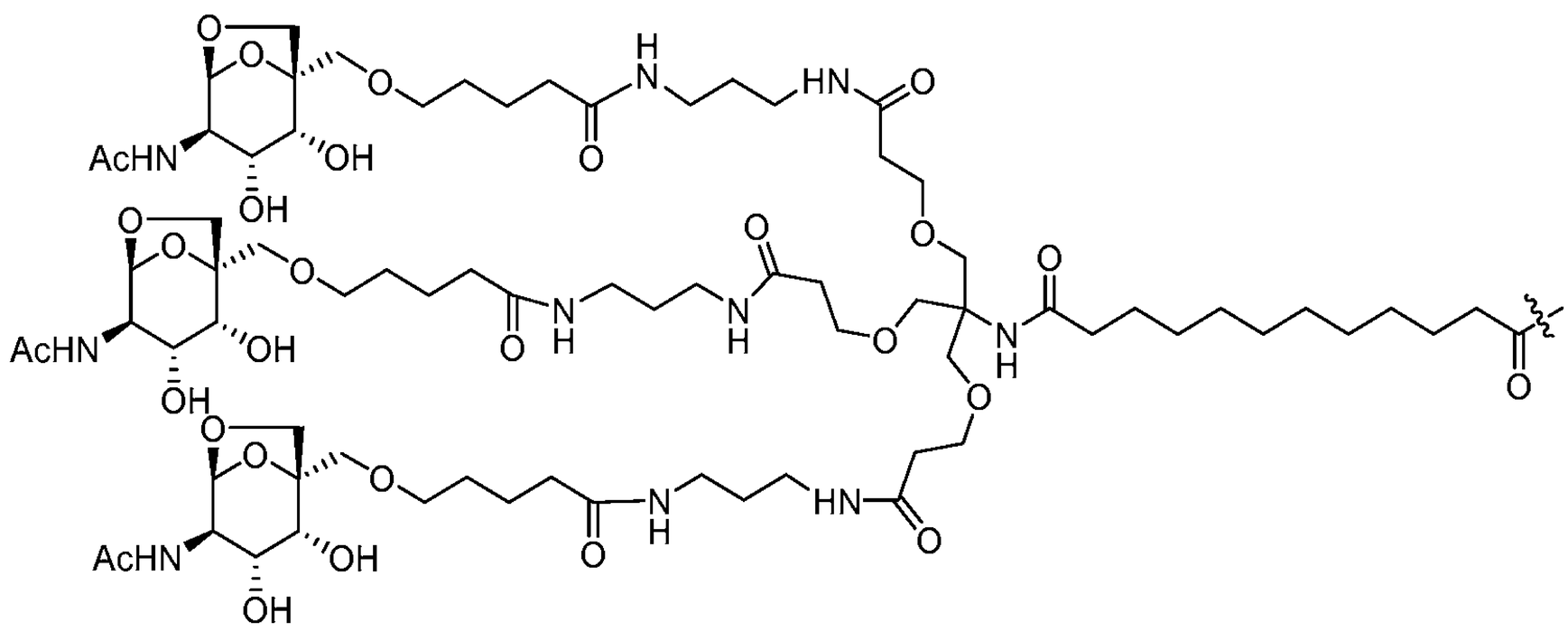
some embodiments, an additional chemical moiety is or comprises  . In some embodiments, an additional chemical moiety is or comprises  .

[00933] In some embodiments, an additional chemical moiety comprises one or more moieties that can bind to, e.g., oligonucleotide target cells. For example, in some embodiments, an additional chemistry moiety comprises one or more protein ligand moieties, e.g., in some embodiments, an additional chemical moiety comprises multiple moieties, each of which independently is an ASGPR ligand. In some embodiments, as in Mod 001 and Mod083, an additional chemical moiety comprises three such ligands.

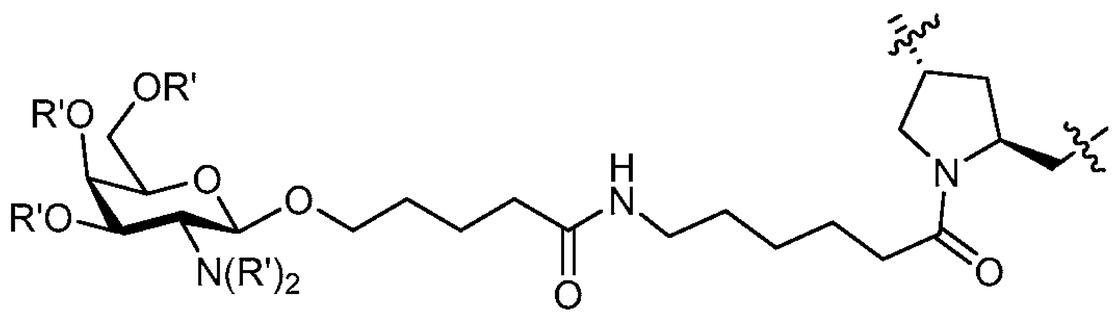
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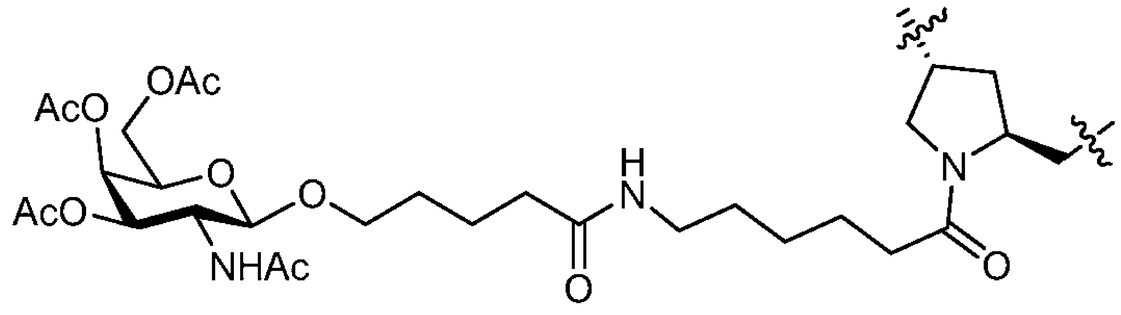
Mod083:



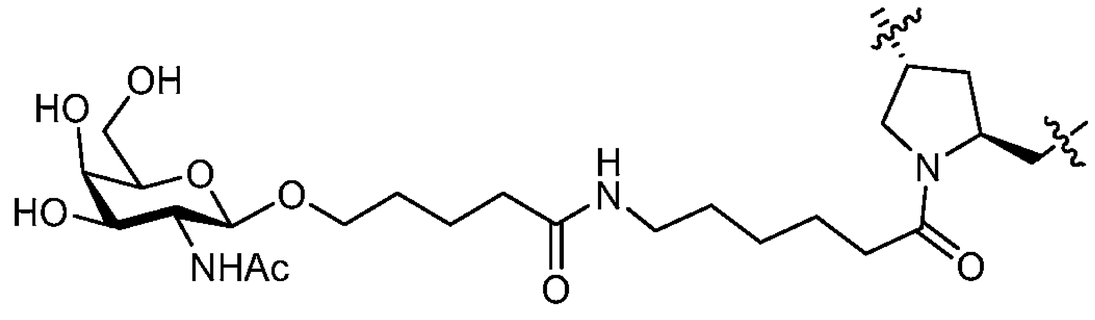
[00934] In some embodiments, an oligonucleotide comprises



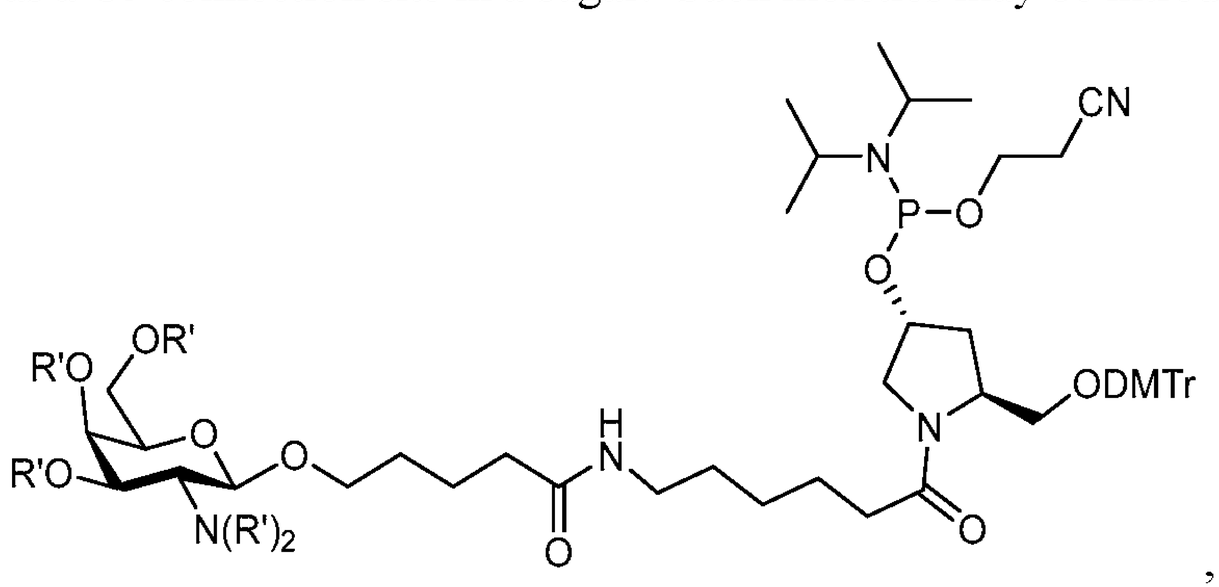
, wherein each variable is independently as described herein. In some embodiments, each −OR' is −OAc, and −N(R')$_2$ is −NHAc. In some embodiments, an oligonucleotide comprises



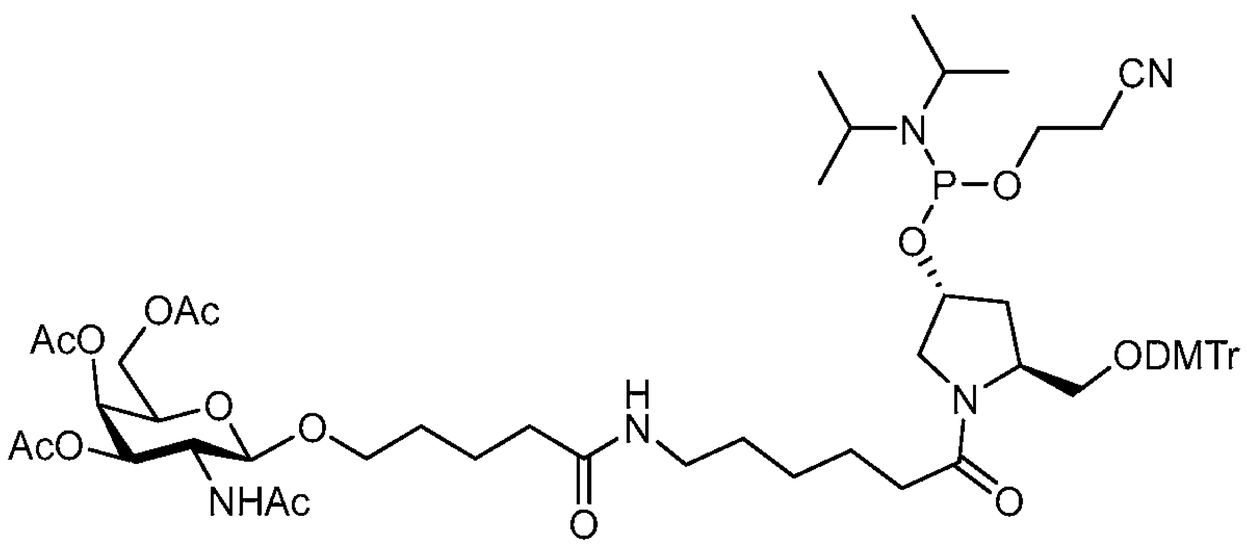
. In some embodiments, each R' is −H. In some embodiments, each −OR' is −OH, and each −N(R')$_2$ is −NHC(O)R. In some embodiments, each −OR' is −OH, and each −N(R')$_2$ is −NHAc. In some embodiments, an oligonucleotide comprises



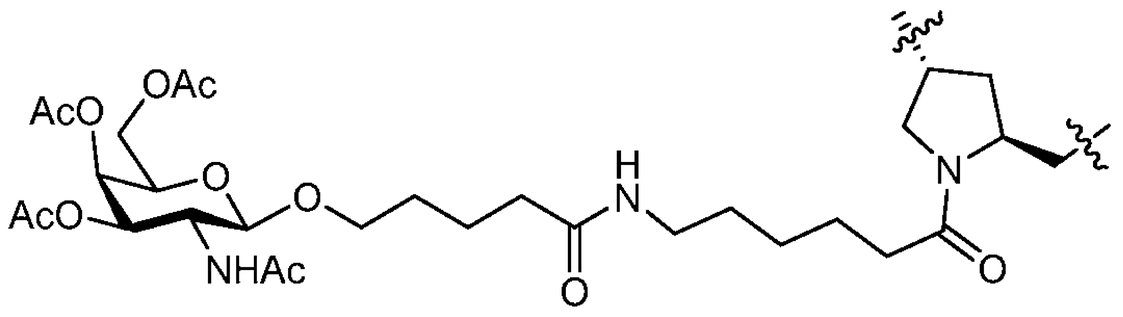
(L025). In some embodiments, the −CH_2− connection site is utilized as a C5 connection site in a sugar. In some embodiments, the connection site on the ring is utilized as a C3 connection site in a sugar. Such moieties may be introduced utilizing, e.g., phosphoramidites such as



, e.g.,

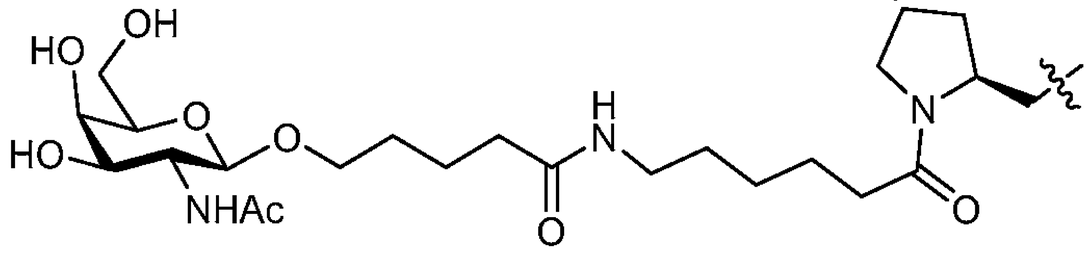


(those skilled in the art appreciate that one or more other groups, such as protection groups for −OH, −NH_2−, −N(i-Pr)$_2$, −OCH_2CH_2CN, etc., may be alternatively utilized, and protection groups can be removed under various suitable conditions, sometimes during oligonucleotide de-protection and/or cleavage steps). In some embodiments, an oligonucleotide

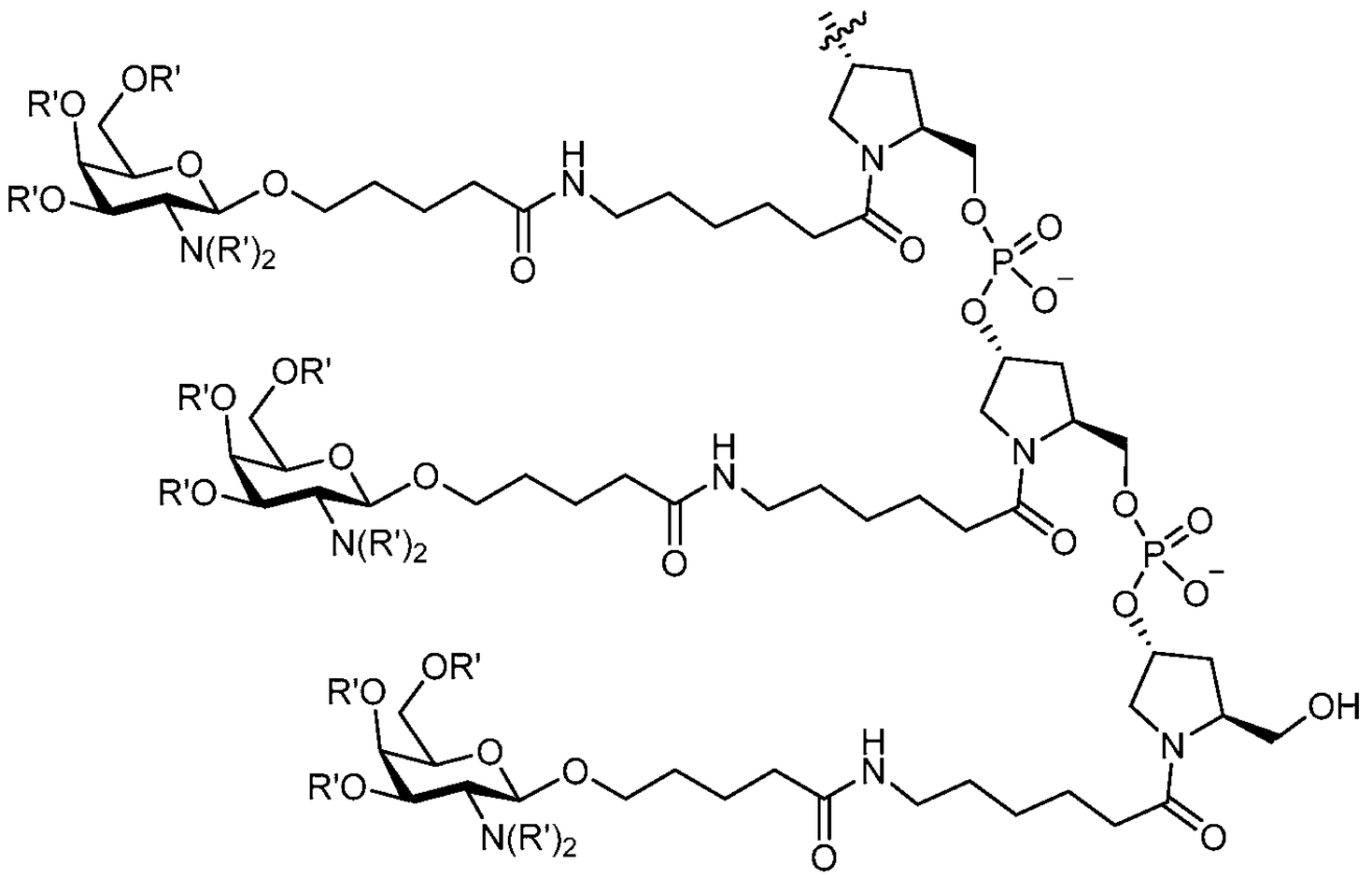


comprises 2, 3 or more (e.g., 3 and no more than 3)

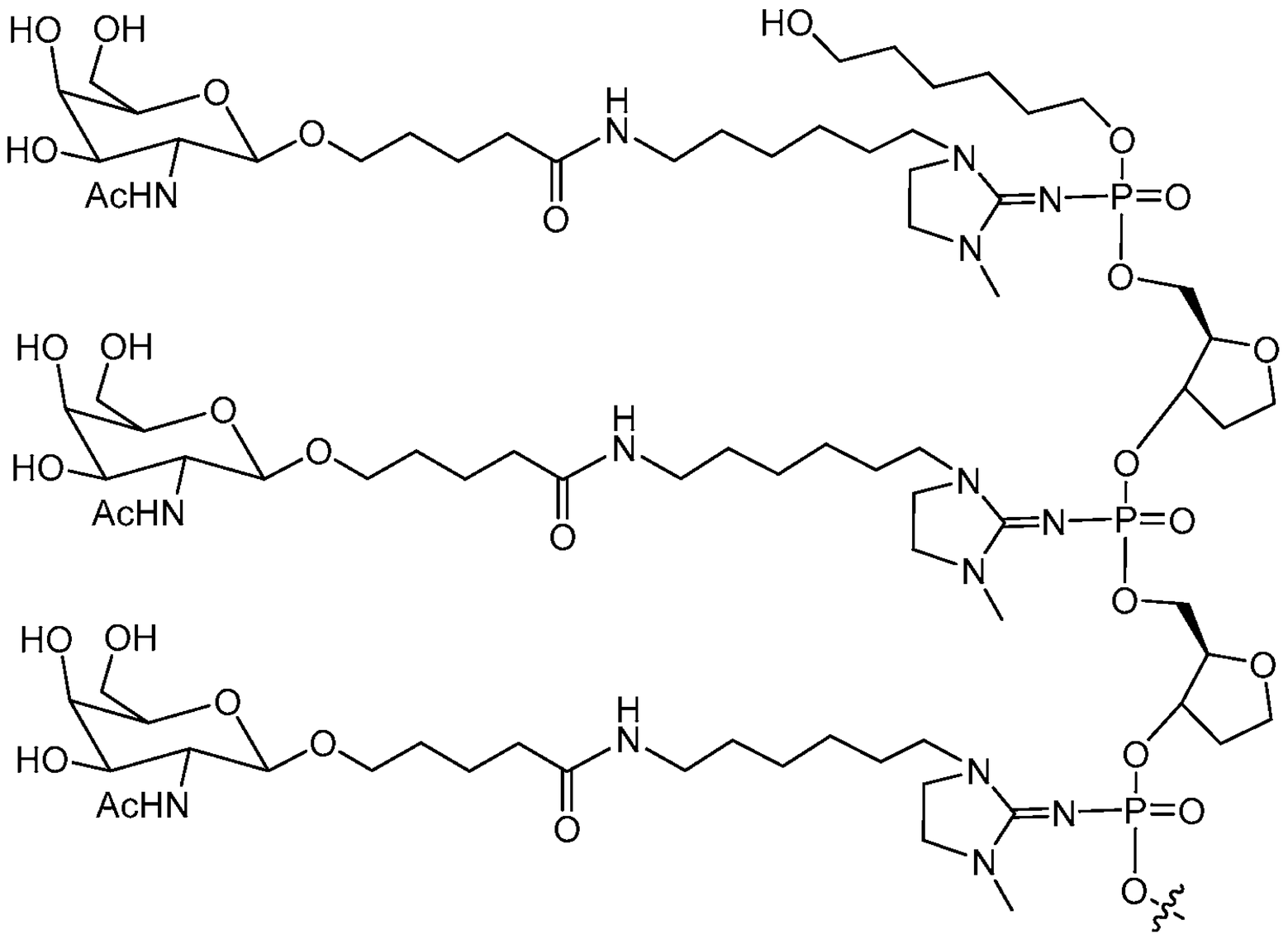
. In some embodiments, an oligonucleotide comprises 2, 3 or more (e.g., 3 and no more than 3)



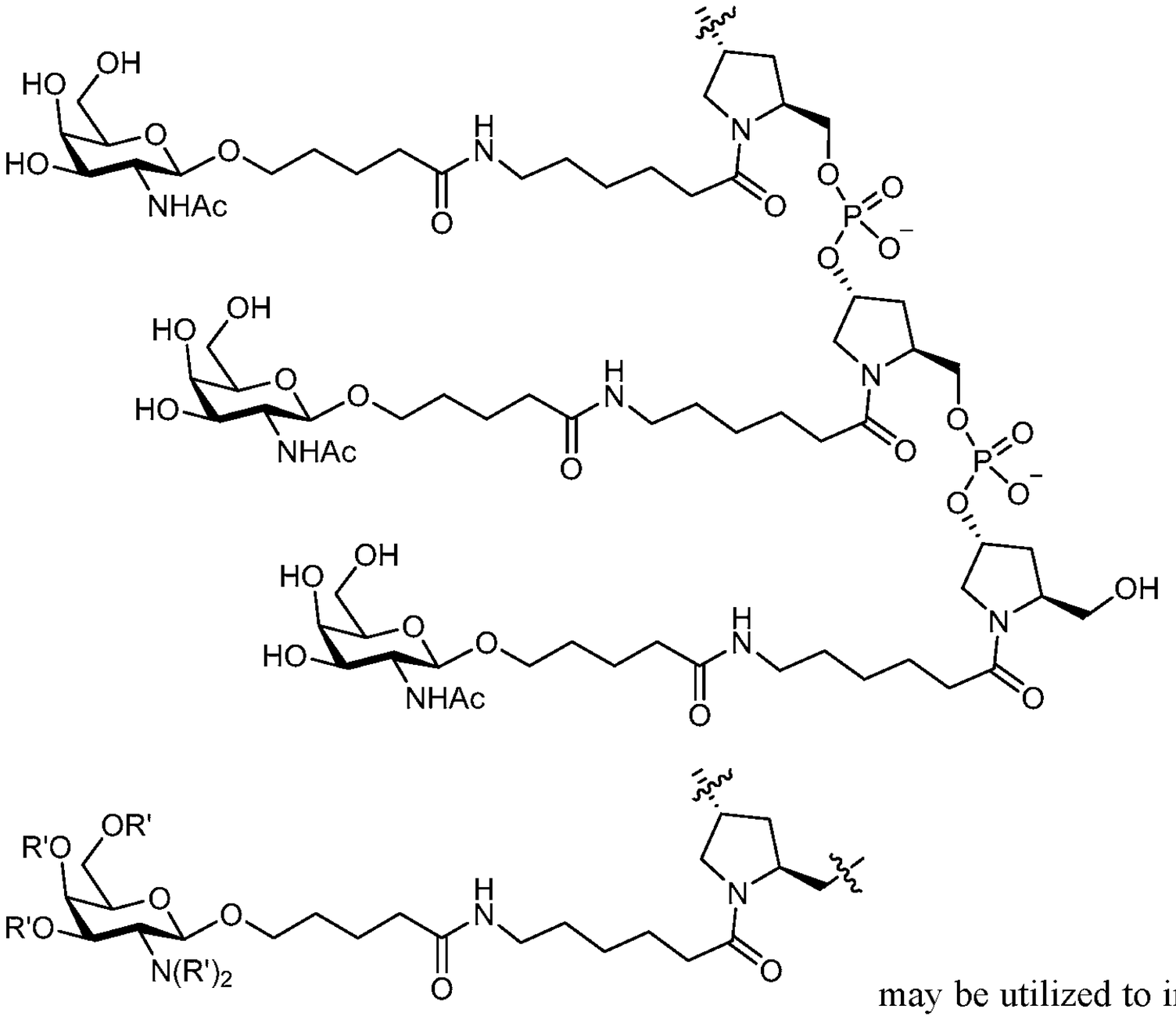
. In some embodiments, copies of such moieties are linked by internucleotidic linkages, e.g., natural phosphate linkages, as described herein. In some embodiments, when at a 5'-end, a $-CH_2-$ connection site is bonded to $-OH$. In some embodiments, an



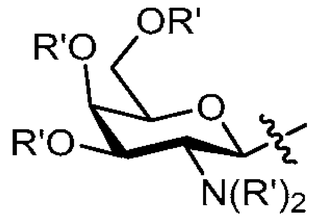
oligonucleotide comprises . In some embodiments, an oligonucleotide comprises



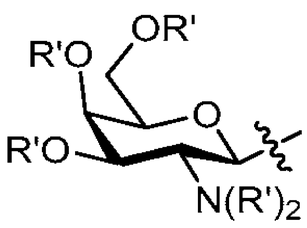
. In some embodiments, each −OR' is −OAc, and −N(R')$_2$ is −NHAc. In some embodiments, an oligonucleotide comprises



. Among other things,



may be utilized to introduce with comparable and/or better activities and/or properties. In some embodiments, it provides improved preparation



efficiency and/or lower cost for the same number of (e.g., when compared to Mod001).

[00935] In some embodiments, an additional chemical moiety is a Mod group described herein, e.g., in Table 1.

[00936] In some embodiments, an additional chemical moiety is Mod001. In some embodiments, an additional chemical moiety is Mod083. In some embodiments, an additional chemical moiety, e.g., a Mod group, is directly conjugated (e.g., without a linker) to the remainder of the oligonucleotide. In some embodiments, an additional chemical moiety is conjugated via a linker to the remainder of the oligonucleotide. In some embodiments, additional chemical moieties, e.g., Mod groups, may be directly connected, and/or via a linker, to nucleobases, sugars and/or internucleotidic linkages of oligonucleotides. In some embodiments, Mod groups are connected, either directly or via a linker, to sugars. In some embodiments, Mod groups are connected, either directly or via a linker, to 5'-end sugars. In some embodiments, Mod groups are connected, either directly or via a linker, to 5'-end sugars via 5' carbon. For examples, see various oligonucleotides in Table 1. In some embodiments, Mod groups are connected, either directly or via a linker, to 3'-end sugars. In some embodiments, Mod groups are connected, either directly or via a linker, to 3'-end sugars via 3' carbon. In some embodiments, Mod groups are connected, either directly or via a linker, to nucleobases. In some embodiments, Mod groups are connected, either directly or via a linker, to internucleotidic linkages. In some embodiments, provided oligonucleotides comprise Mod001 connected to 5'-end of oligonucleotide chains through L001.

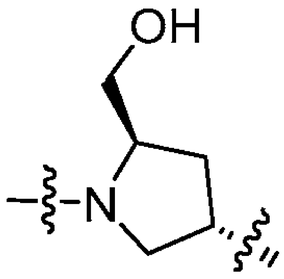
[00937] As appreciated by those skilled in the art, an additional chemical moiety may be connected to an oligonucleotide chain at various locations, e.g., 5'-end, 3'-end, or a location in the middle (e.g., on a sugar, a base, an internucleotidic linkage, etc.). In some embodiments, it is connected at a 5'-end. In some embodiments, it is connected at a 3'-end. In some embodiments, it is connected at a nucleotide in the middle.

[00938] Certain additional chemical moieties (e.g., lipid moieties, targeting moieties, carbohydrate moieties), including but not limited to Mod012, Mod039, Mod062, Mod085, Mod086, and Mod094, and various linkers for connecting additional chemical moieties to oligonucleotide chains, including but not limited to L001, L003, L004, L008, L009, and L010, are described in WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the additional chemical moieties and linkers of each of which are independently incorporated herein by reference, and can be utilized in accordance with the present disclosure. In some embodiments, an additional chemical moiety is digoxigenin or biotin or a derivative thereof.

[00939] In some embodiments, an oligonucleotide comprises a linker, e.g., L001 L004, L008, and/or an additional chemical moiety, e.g., Mod012, Mod039, Mod062, Mod085, Mod086, or Mod094. In some embodiments, a linker, *e.g.*, L001, L003, L004, L008, L009, L110, *etc.* is linked to a Mod, *e.g.*, Mod012, Mod039, Mod062, Mod085, Mod086, Mod094, *etc.*

L001: $-NH-(CH_2)_6-$ linker (also known as a C6 linker, C6 amine linker or C6 amino linker), connected to

Mod, if any, through −NH−, and the 5'-end or 3'-end of the oligonucleotide chain through either a phosphate linkage (−O−P(O)(OH)−O−, which may exist as a salt form, and may be indicated as O or PO) or a phosphorothioate linkage (−O−P(O)(SH)−O−, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *S*p, if the phosphorothioate is chirally controlled and has an *S*p configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration) as indicated at the $-CH_2-$ connecting site. If no Mod is present, L001 is connected to −H through −NH−;

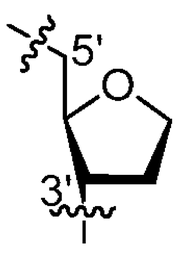
L003:  linker. In some embodiments, it is connected to Mod, if any (if no Mod, −H), through its amino group, and the 5'-end or 3'-end of an oligonucleotide chain e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *Rp*)));

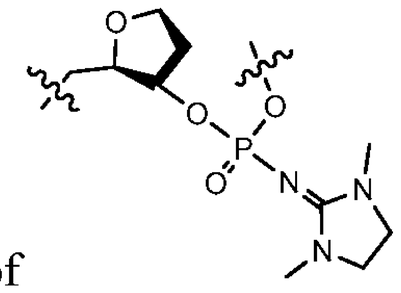
L004: linker having the structure of $-NH(CH_2)_4CH(CH_2OH)CH_2-$, wherein −NH− is connected to Mod (through −C(O)−) or −H, and the $-CH_2-$ connecting site is connected to an oligonucleotide chain (e.g., at the 3'-end) through a linkage, e.g., phosphodiester (−O−P(O)(OH)−O−, which may exist as a salt form, and may be indicated as O or PO), phosphorothioate (−O−P(O)(SH)−O−, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *S*p, if the phosphorothioate is chirally controlled and has an *S*p configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration), or phosphorodithioate (−O−P(S)(SH)−O−, which may exist as a salt form, and may be indicated as PS2 or : or D) linkage. For example, an asterisk immediately preceding a L004 (e.g., *L004) indicates that the linkage is a phosphorothioate linkage, and the absence of an asterisk immediately preceding L004 indicates that the linkage is a phosphodiester linkage. For example, in an oligonucleotide which terminates in ...mAL004, the linker L004 is connected (via the $-CH_2-$ site) through a phosphodiester linkage to the 3' position of the 3'-terminal sugar (which is 2'-OMe modified and connected to the nucleobase A), and the L004 linker is connected via −NH− to −H. Similarly, in one or more oligonucleotides, the L004 linker is connected (via the $-CH_2-$ site) through the phosphodiester linkage to the 3' position of the 3'-terminal sugar, and the L004 is connected via −NH− to, e.g., Mod012, Mod085, Mod086, etc.;

L008: linker having the structure of $-C(O)-(CH_2)_9-$, wherein −C(O)− is connected to Mod (through −NH−) or −OH (if no Mod indicated), and the $-CH_2-$ connecting site is connected to an oligonucleotide chain (e.g., at the 5'-end) through a linkage, e.g., phosphodiester (−O−P(O)(OH)−O−, which may exist as a salt form, and may be indicated as O or PO), phosphorothioate (−O−P(O)(SH)−O−, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *S*p, if the phosphorothioate is chirally controlled and has an *S*p configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration), or phosphorodithioate (−O−P(S)(SH)−O−, which may exist as a salt form, and

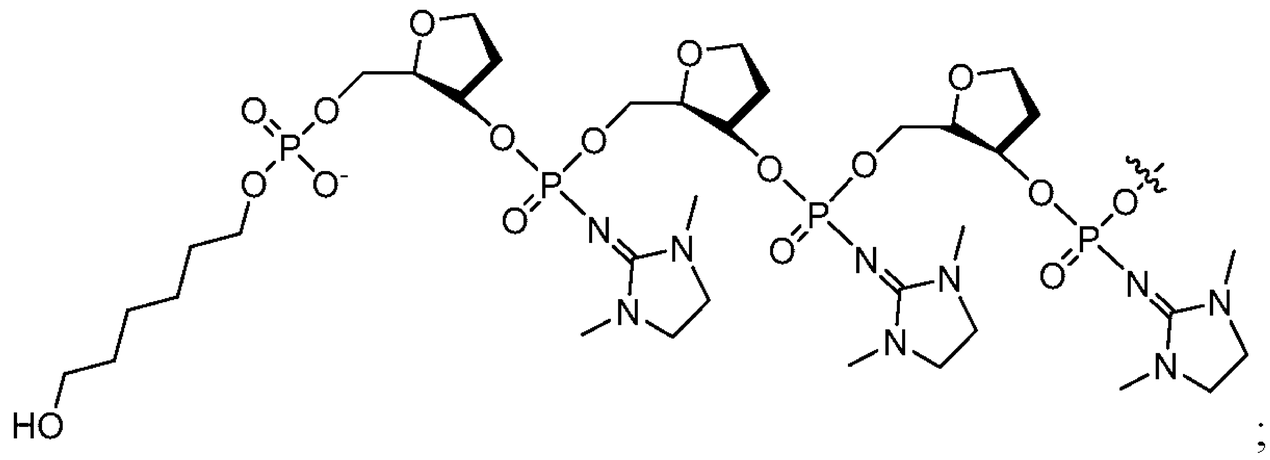
may be indicated as PS2 or : or D) linkage. For example, in an example oligonucleotide which has the sequence of 5'-L008mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mN-3', and which has a Stereochemistry/Linkage of OXXXXXXXXX XXXXXXXX, wherein N is a base, wherein O is a natural phosphate internucleotidic linkage, and wherein X is a stereorandom phosphorothioate, L008 is connected to −OH through −C(O)−, and the 5'-end of an oligonucleotide chain through a phosphate linkage (indicated as "O" in "Stereochemistry/Linkage"); in another example oligonucleotide, which has the sequence of 5'-Mod062L008mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mN-3', and which has a Stereochemistry/Linkage of OXXXXXXXXX XXXXXXXX, wherein N is a base, L008 is connected to Mod062 through −C(O)−, and the 5'-end of an oligonucleotide chain through a phosphate linkage (indicated as "O" in "Stereochemistry/Linkage");

L009: $-CH_2CH_2CH_2-$. In some embodiments, when L009 is present at the 5'-end of an oligonucleotide without a Mod, one end of L009 is connected to −OH and the other end connected to a 5'-carbon of the oligonucleotide chain e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *Rp*)));

L010: 

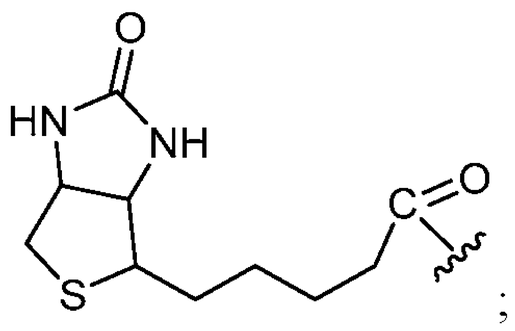
. L010 connects to other moieties, e.g., L023, L010, oligonucleotide chains, etc., through various linkages (e.g., n001; if not indicated, typically phosphates). When no other moieties are present, L010 is bonded to −OH. For example in WV-39202, L010 is utilized with n001R to form L010n001R, which has the structure of 

and wherein the configuration of linkage phosphorus is *R*p. In some embodiments, multiple L010n001R may be utilized. For example, WV-39202 comprises L023L010n001RL010n001RL010n001R, which has the following structure (which is bonded to the 5'-carbon at the 5'-end of the oligonucleotide chain, and each linkage phosphorus is independently *R*p):



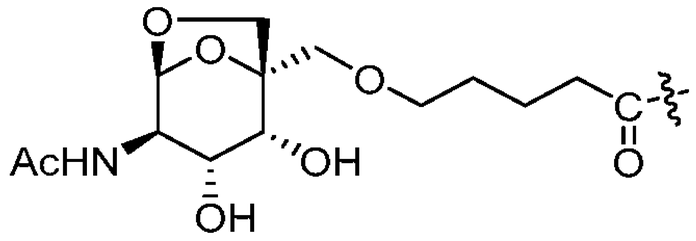
;

Mod012 (in some embodiments, −C(O)− connects to −NH− of a linker such as L001, L004, L008, *etc.*):

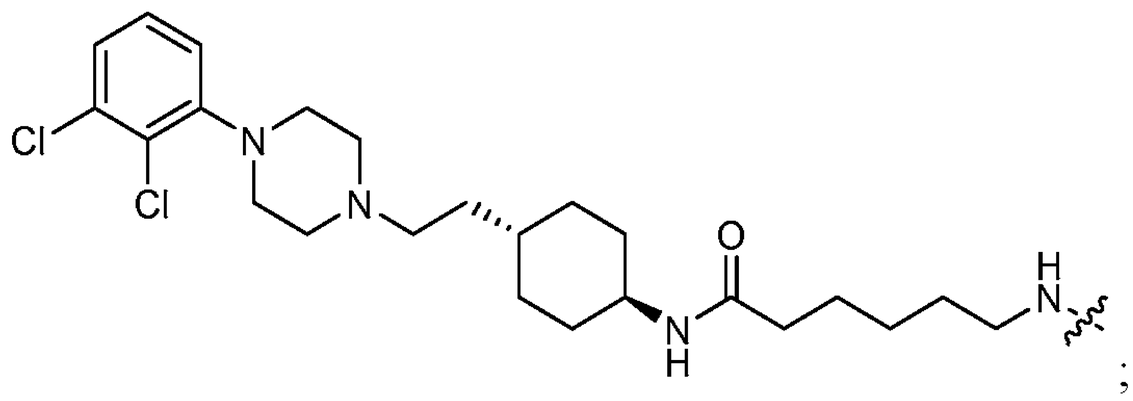


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Mod039 (in some embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):

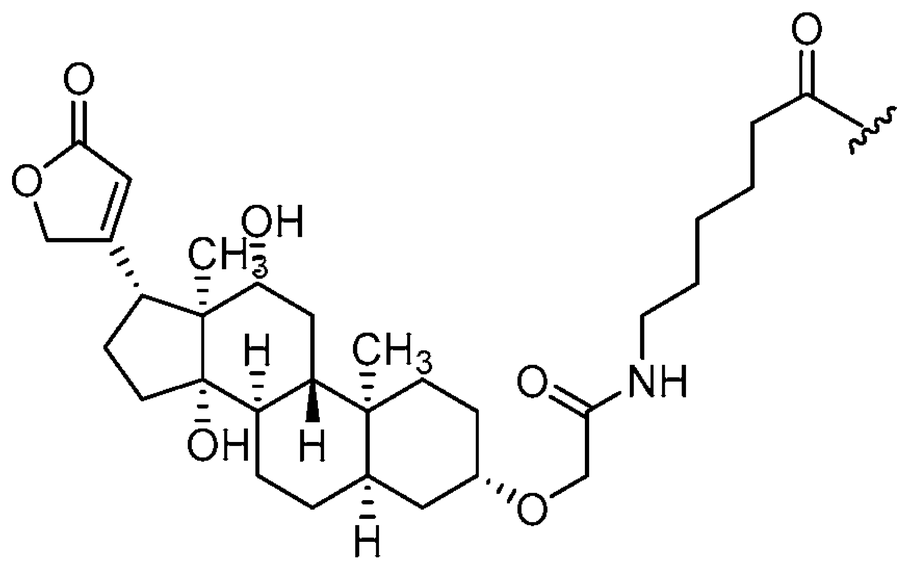


Mod062 (in some embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



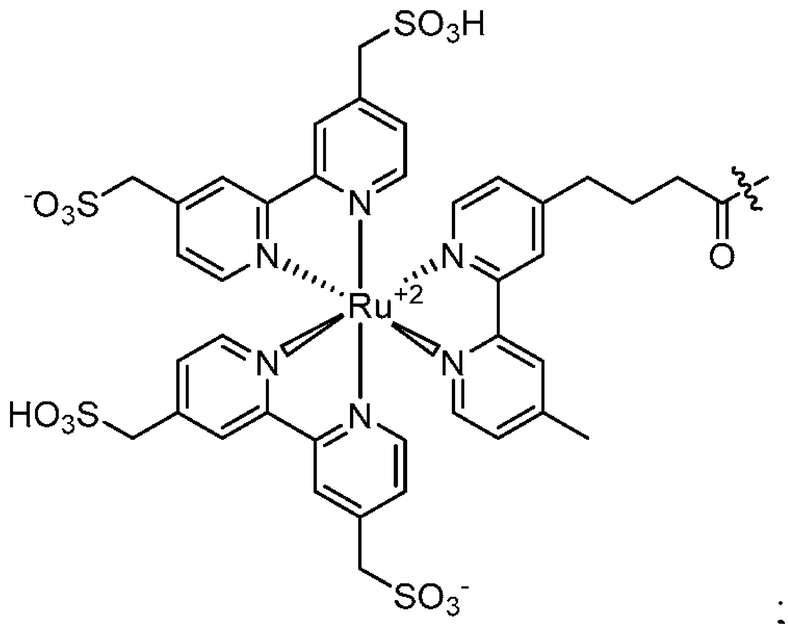
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Mod085 (in some embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):

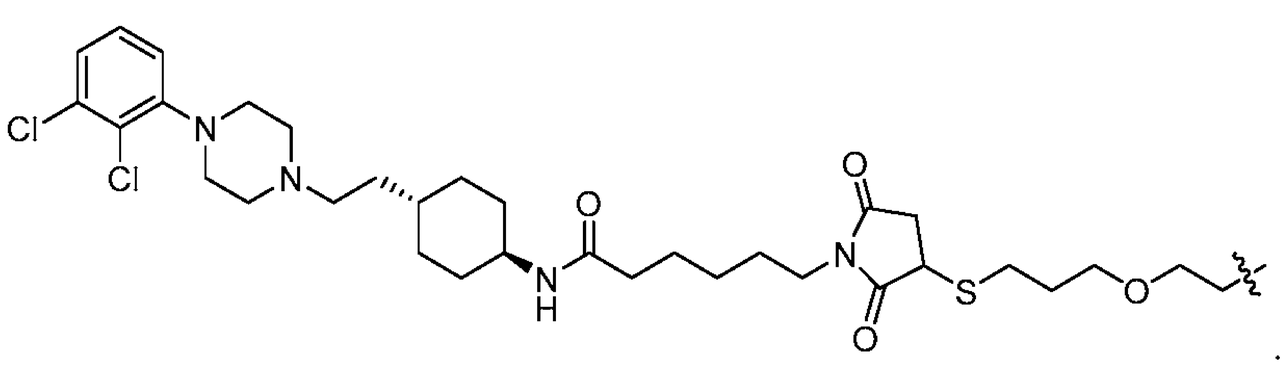


;

Mod086 (in some embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



Mod094 (in some embodiments, connects to an internucleotidic linkage, or to the 5'-end or 3'-end of an oligonucleotide via a linkage, *e.g.*, a phosphate linkage, a phosphorothioate linkage (which is optionally chirally controlled), *etc.*. For example, in an example oligonucleotide which has the sequence of 5'-mN * mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mNMod094-3', and which has a Stereochemistry/Linkage of XXXXX XXXXX XXXXX XXO, wherein N is a base, Mod094 is connected to the 3'-end of the oligonucleotide chain (3'-carbon of the 3'-end sugar) through a phosphate group (which is not shown below and which may exist as a salt form; and which is indicated as "O" in "Stereochemistry/Linkage" (...XXXX**O**))):



[00940] In some embodiments, an additional chemical moiety (e.g., a linker, lipid, solubilizing group, conjugate group, targeting group, and/or targeting ligand) is one described in WO 2012/030683 or WO 2021/030778. In some embodiments, a provided oligonucleotide comprise a chemical structure (e.g. , a linker, lipid, solubilizing group, and/or targeting ligand) described in WO 2012/030683, WO 2021/030778, WO 2019112485, US 20170362270, WO 2018156056, or WO 2018056871, WO 2021/030778, WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376.

[00941] In some embodiments, a provide oligonucleotide comprises an additional chemical moiety (e.g., a targeting group, a conjugate group, etc.) and/or a modification (e.g., of nucleobase, sugar, internucleotidic linkage, etc.) described in: U.S. Pat. Nos. 5,688,941; 6,294,664; 6,320,017; 6,576,752; 5,258,506; 5,591,584; 4,958,013; 5,082,830; 5,118,802; 5,138,045; 6,783,931; 5,254,469; 5,414,077; 5,486,603; 5,112,963; 5,599,928; 6,900,297; 5,214,136; 5,109,124; 5,512,439; 4,667,025; 5,525,465; 5,514,785; 5,565,552; 5,541,313; 5,545,730; 4,835,263; 4,876,335; 5,578,717; 5,580,731; 5,451,463; 5,510,475; 4,904,582; 5,082,830; 4,762,779; 4,789,737; 4,824,941; 4,828,979; 5,595,726; 5,214,136; 5,245,022; 5,317,098; 5,371,241; 5,391,723; 4,948,882; 5,218,105; 5,112,963; 5,567,810; 5,574,142; 5,578,718; 5,608,046;

4,587,044; 4,605,735; 5,585,481; 5,292,873; 5,552,538; 5,512,667; 5,597,696; 5,599,923; 7,037,646; 5,587,371; 5,416,203; 5,262,536; 5,272,250; or 8,106,022.

[00942] In some embodiments, an additional chemical moiety, e.g., a Mod, is connected via a linker. Various linkers are available in the art and may be utilized in accordance with the present disclosure, for example, those utilized for conjugation of various moieties with proteins (e.g., with antibodies to form antibody-drug conjugates), nucleic acids, etc. Certain useful linkers are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the linker moieties of each which are independently incorporated herein by reference. In some embodiments, a linker is, as non-limiting examples, L001, L004, L009 or L010. In some embodiments, an oligonucleotide comprises a linker, but not an additional chemical moiety other than the linker. In some embodiments, an oligonucleotide comprises a linker, but not an additional chemical moiety other than the linker, wherein the linker is L001, L004, L009, or L010. In some embodiments, a linker is or comprises a moiety having the structure of an internucleotidic linkage as described herein. In some embodiments, such a moiety in a linker does not connect two nucleosides. In some embodiments, a linker has the structure of L. In some embodiments, a linker is bivalent. In some embodiments, a linker is polyvalent. In some embodiments, a linker can connect two or more additional chemical moieties to an oligonucleotide chain as described herein. For example, some embodiments, one or two or three or more additional chemical moieties, e.g., GalNAc moieties, are connected to an oligonucleotide chain (e.g., at 5'-end) through a multivalent linker moiety.

[00943] In some embodiments, an additional chemical moiety is cleaved from the remainder of an oligonucleotide, e.g., an oligonucleotide chain, e.g., after administration to a system, cell, tissue, organ, subject, etc. In some embodiments, additional chemical moieties promote, increase, and/or accelerate delivery to certain cells, and after delivery of oligonucleotides into such cells, additional chemical moieties are cleaved from oligonucleotides. In some embodiments, linker moieties comprise one or more cleavable moieties that can be cleaved at desirable locations (e.g., within certain type of cells, subcellular compartments such as lysosomes, etc.) and/or timing. In some embodiments, a cleavable moiety is selectively cleaved by a polypeptide, e.g., an enzyme such as a nuclease. Many useful cleavable moieties and cleavable linkers are reported and can be utilized in accordance with the present disclosure. In some embodiments, a cleavable moiety is or comprises one or more functional groups selected from amide, ester, ether, phosphodiester, disulfide, carbamate, etc. In some embodiments, a linker is as described in WO 2012/030683, WO 2021/030778, WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376.

[00944] As demonstrated herein, provided technologies can provide high levels of activities and/or desired properties, in some embodiments, without utilizing particular structural elements (e.g., modifications, linkage

configurations and/or patterns, etc.) reported to be desired and/or necessary (e.g., those reported in WO 2019/219581), though certain such structural elements may be incorporated into oligonucleotides in combination with various other structural elements in accordance with the present disclosure. For example, in some embodiments, oligonucleotides of the present disclosure have fewer nucleosides 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine), contain one or more phosphorothioate internucleotidic linkages at one or more positions where a phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, contain one or more Sp phosphorothioate internucleotidic linkages at one or more positions where a Sp phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, contain one or more Rp phosphorothioate internucleotidic linkages at one or more positions where a Rp phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, and/or contain different modifications (e.g., internucleotidic linkage modifications, sugar modifications, etc.) and/or stereochemistry at one or more locations compared to those reportedly favorable or required for certain oligonucleotide properties and/or activities (e.g., presence of 2'-MOE, absence of phosphorothioate linkages at certain positions, absence of *S*p phosphorothioate linkages at certain positions, and/or absence of *R*p phosphorothioate linkages at certain positions were reportedly favorable or required for certain oligonucleotide properties and/or activities; as demonstrated herein, provided technologies can provide desired properties and/or high activities without utilizing 2'-MOE, without avoiding phosphorothioate linkages at one or more such certain positions, without avoiding *S*p phosphorothioate linkages at one or more such certain positions, and/or without avoiding *R*p phosphorothioate linkages at one or more such certain positions). Additionally or alternatively, provided oligonucleotides incorporates structural elements that were not previously recognized such as utilization of certain modifications (e.g., base modifications, sugar modifications (e.g., 2'-F), linkage modifications (e.g., non-negatively charged internucleotidic linkages), additional moieties, etc.) and levels, patterns, and combinations thereof.

[00945] For example, in some embodiments, as described herein, provided oligonucleotides contain no more than 5, 6, 7, 8, 9, 10, 11 or 12 nucleosides 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine).

[00946] Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), for structural elements 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine), in some embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%) of internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a modified internucleotidic linkage, which is optionally chirally controlled. In some embodiments, no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside are natural phosphate linkages. In some embodiments, no such internucleotidic linkage is natural phosphate linkages. In some embodiments, no more than 1 such internucleotidic linkage is natural phosphate linkages. In some embodiments, no more than 2 such internucleotidic linkages are natural phosphate linkages. In some embodiments, no more than 3 such internucleotidic linkages are natural phosphate linkages. In some

embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage (e.g., n001). In some embodiments, each phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside are *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage bonded to a nucleoside opposite to a target nucleoside at the 3'-position of its sugar (considered a -1 position) is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, it is the only *R*p phosphorothioate internucleotidic linkage 3' to a nucleoside opposite to a target nucleoside. In some embodiments, an internucleotidic linkage at position -3 relative to a nucleoside opposite to a target nucleoside (e.g., for $\ldots N_0N\text{-}_1N\text{-}_2N\text{-}_3\ldots$, the internucleotidic linkage linking $N\text{-}_2$ and $N\text{-}_3$ wherein N_0 is a nucleoside opposite to a target nucleoside) is not a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -6 relative to a nucleoside opposite to a target nucleoside is not a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position -4 and/or -5 relative to a nucleoside opposite to a target nucleoside is independently a modified internucleotidic linkage, e.g., a phosphorothioate internucleotidic linkage, or is independently a *R*p phosphorothioate internucleotidic linkage. In some embodiments, one or more or all internucleotidic linkages at positions -1, -3, -4, -5, and -6 are each independently a *S*p internucleotidic linkage. In some embodiments, one or more or all internucleotidic linkages at positions -1, -3, -4, -5, and -6 are each independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, internucleotidic linkage(s) at position(s) -4 and/or -5 are each independently a *R*p internucleotidic linkage. In some embodiments, internucleotidic linkage(s) at position(s) -4 and/or -5 are each independently a *R*p phosphorothioate internucleotidic linkage. In many embodiments, no more than 1, 2, 3, 4, or 5 internucleotidic linkages are *R*p phosphorothioate internucleotidic linkage.

[00947] Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), in some embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a modified internucleotidic linkage, which is optionally chirally controlled. In some embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not modified internucleotidic linkages. In some embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not phosphorothioate internucleotidic linkages. In some embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not *S*p phosphorothioate internucleotidic linkages. In some embodiments, no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are natural phosphate linkages. In some embodiments, no such internucleotidic linkage is natural phosphate linkages. In some embodiments, no more than 1 such internucleotidic linkage is natural phosphate linkages. In some embodiments, no more than 2 such internucleotidic linkages are natural phosphate linkages. In some

embodiments, no more than 3 such internucleotidic linkages are natural phosphate linkages. In some embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage (e.g., n001). In some embodiments, there are no 2, 3, or 4 consecutive internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside, each of which is not a phosphorothioate internucleotidic linkage. In some embodiments, there are no 2, 3, or 4 consecutive internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside, each of which is chirally controlled and is not a *S*p phosphorothioate internucleotidic linkage. In some embodiments, no or no more than 1, 2, 3, 4, or 5 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage bonded to a nucleoside opposite to a target nucleoside at the 5'-position of its sugar (considered a +1 position) is a *R*p phosphorothioate internucleotidic linkage. In some embodiments, it is the only *R*p phosphorothioate internucleotidic linkage 3' to a nucleoside opposite to a target nucleoside. In some embodiments, an internucleotidic linkage at position +5 relative to a nucleoside opposite to a target nucleoside (e.g., for $\ldots N_{+5}N_{+4}N_{+3}N_{+2}N_{+1}N_0\ldots$, the internucleotidic linkage linking N_{+4} and N_{+5} wherein N_0 is a nucleoside opposite to a target nucleoside) is not a *R*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at positions +11 is not a *S*p phosphorothioate internucleotidic linkage. In some embodiments, one or more or all internucleotidic linkages at positions +6 to +8 relative to a nucleoside opposite to a target nucleoside are each independently a modified internucleotidic linkage, optionally chirally controlled. In some embodiments, each of them is independently a phosphorothioate internucleotidic linkage. In some embodiments, each of them is independently a *S*p phosphorothioate internucleotidic linkage. In some embodiments, one or more or all internucleotidic linkages at positions +6 to +8 relative to a nucleoside opposite to a target nucleoside are each independently a phosphorothioate internucleotidic linkage, optionally chirally controlled. In some embodiments, one or more or all internucleotidic linkages at positions +6, +7, +8, +9, and +11 are each independently *R*p internucleotidic linkages. In some embodiments, one or more or all internucleotidic linkages at positions +6, +7, +8, +9, and +11 are each independently *R*p phosphorothioate internucleotidic linkages. In some embodiments, one or more or all internucleotidic linkages at positions +5, +6, +7, +8, and +9 relative to a nucleoside opposite to a target adenosine are each independently *S*p internucleotidic linkages. In some embodiments, one or more or all internucleotidic linkages at positions +5, +6, +7, +8, and +9 relative to a nucleoside opposite to a target adenosine are each independently *S*p phosphorothioate internucleotidic linkages. In some embodiments, an internucleotidic linkage at position +5 is a *S*p internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +5 is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +6 is a *S*p internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +6 is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +7 is a *S*p internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +7 is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +8 is

a *S*p internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +8 is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +9 is a *S*p internucleotidic linkage. In some embodiments, an internucleotidic linkage at position +9 is a *S*p phosphorothioate internucleotidic linkage. In some embodiments, at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32, or about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently chirally controlled and a *S*p internucleotidic linkage. In some embodiments, at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32, or about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently chirally controlled and are *S*p. In some embodiments, each phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) is chirally controlled. In some embodiments, each phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) is *S*p.

[00948] Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), in some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently a natural phosphate linkage. In some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are independently a natural phosphate linkage. In some embodiments, one or more, e.g., about 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 5-6, 5-7, 5-8, 5-9, 5-10, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, internucleotidic linkages in an oligonucleotide are independently a natural phosphate linkage. In some embodiments, one or more, e.g., about 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 5-6, 5-7, 5-8, 5-9, 5-10, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are independently a natural phosphate linkage. In some embodiments, one or more internucleotidic linkages at one or more of positions +3 (between $N_{+4}N_{+3}$), +4, +6, +8, +9, +12, +14, +15, +17, and +18 are independently a natural phosphate linkage. In some embodiments, there are 4 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 5 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 6 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 7 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 8 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 9 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments,

there are 10 natural phosphate linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, one or more internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a natural phosphate linkage. In some embodiments, there is one natural phosphate linkage 3' to a nucleoside opposite to a target nucleoside. In some embodiments, an internucleotidic linkage at position -3 is a natural phosphate linkage.

[00949] Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), in some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, 30%-70%, 40-70%, 40%-65%, 40%-60%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or 65% of all internucleotidic linkages in an oligonucleotide are independently a phosphorothioate internucleotidic linkage. In some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, 30%-70%, 40-70%, 40%-65%, 40%-60%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or 65% of all internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are independently a natural phosphate linkage. In some embodiments, one or more, e.g., about 1-30, 1-25, 1-20, 1-15, 5-30, 5-25, 5-20, 5-15, 10-30, 10-25, 10-20, 10-15, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, internucleotidic linkages in an oligonucleotide are independently a phosphorothioate internucleotidic linkage. In some embodiments, one or more, e.g., about 1-30, 1-25, 1-20, 1-15, 5-30, 5-25, 5-20, 5-15, 10-30, 10-25, 10-20, 10-15, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are independently a phosphorothioate internucleotidic linkage. In some embodiments, one or more internucleotidic linkages at one or more of positions +1 (between $N_{+1}N_0$), +2, +5, +6, +7, +8, +11, +14, +15, +16, +17, +19, +20, +21, and +22 are independently a phosphorothioate internucleotidic linkage. In some embodiments, there are 5 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 10 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 11 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 12 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 13 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 14 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 15 or more phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, one or more internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a phosphorothioate internucleotidic linkage. In some embodiments, there is one phosphorothioate internucleotidic linkage 3' to a nucleoside opposite to a target nucleoside. In some embodiments, there are two phosphorothioate internucleotidic linkages 3' to a nucleoside

opposite to a target nucleoside. In some embodiments, there are three phosphorothioate internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside. In some embodiments, one or more or all internucleotidic linkages at positions -1, -4 and -5 are independently a phosphorothioate internucleotidic linkage. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, about or at least about 80%, 85%, 90% or 95% of all phosphorothioate internucleotidic linkages are independently *S*p. In some embodiments, each phosphorothioate internucleotidic linkage is independently *S*p.

[00950] Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), in some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently a non-negatively charged internucleotidic linkage. In some embodiments, about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a non-negatively charged internucleotidic linkage. In some embodiments, one or more, e.g., about 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 5-6, 5-7, 5-8, 5-9, 5-10, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, internucleotidic linkages in an oligonucleotide is independently a non-negatively charged internucleotidic linkage. In some embodiments, one or more, e.g., about 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 5-6, 5-7, 5-8, 5-9, 5-10, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) is independently a non-negatively charged internucleotidic linkage. In some embodiments, one or more internucleotidic linkages at one or more or all of positions +5 (between $N_{+5}N_{+4}$), +10, +13 or +23 are independently a non-negatively charged internucleotidic linkage. In some embodiments, there are 2 or more non-negatively charged internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 3 or more non-negatively charged internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 4 or more non-negatively charged internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, there are 5 or more non-negatively charged internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside. In some embodiments, one or more internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a non-negatively charged internucleotidic linkage. In some embodiments, there is one non-negatively charged internucleotidic linkage 3' to a nucleoside opposite to a target nucleoside. In some embodiments, there are two or more non-negatively charged internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside. In some embodiments, there are two non-negatively charged internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside. In some embodiments, one or both internucleotidic linkages at positions -2 and -6 are independently a non-negatively charged internucleotidic linkage. In some embodiments, a non-

negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is independently a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, each non-negatively charged internucleotidic linkage is independently a phosphoryl guanidine internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, each non-negatively charged internucleotidic linkage is independently n001. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage is independently chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is *R*p. In some embodiments, a non-negatively charged internucleotidic linkage is *S*p. In some embodiments, each non-negatively charged internucleotidic linkage is independently *S*p. In some embodiments, each n001 is independently *S*p except that each n001 bonded to 3'-carbon of dI is independently *R*p.

ADAR

[00951] Among other things, provided technologies can provide modification/editing of target adenosine by converting A to I. In some embodiments, oligonucleotides and/or duplexes formed by oligonucleotides with target nucleic acids interact with proteins, e.g., ADAR proteins. In some embodiments, such proteins comprise adenosine modifying activities and can modify target adenosine in target nucleic acids, e.g., converting them to inosine.

[00952] ADAR proteins are naturally expressed proteins in various cells, tissues, organs and/or organism. It has been reported that some ADAR proteins, e.g.,, ADAR1 and ADAR2, can edit adenosine through deamination, converting adenosine to inosine which can provide a number of functions including being read as or similar to G during translation. Mechanism of ADAR-mediated mRNA editing (e.g., deamination) has been reported. For example, ADAR proteins are reported to catalyze conversion of adenosine to inosine on double-stranded RNA substrates with mismatches. As appreciated by those skilled in the art, inosine can be recognized as guanosine by cellular translation and/or splicing machinery. ADAR can thus be used for functional adenosine to guanosine editing of nucleic acids, e.g., pre-mRNA and mRNA substrates.

[00953] In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for ADAR-mediated editing of target adenosine in target nucleic acids, e.g. RNA. ADAR-mediated RNA-editing can offer several advantages over DNA-editing, e.g., delivery is simplified as expression of recombinant proteins like Cas9 is not required. Both ADAR1 and ADAR2 are endogenous enzymes, so cellular delivery of oligonucleotides alone can be sufficient for editing. Off-target effects, if any, are transient and changes are not made to genomic DNA. Additionally, ADAR-mediated editing can be used in post-mitotic cells and it does not require an HDR-template for repair. Three vertebrate ADAR genes have been reported with common functional domains (Nishikura Nat Rev Mol Cell Biol. 2016 Feb; 17(2): 83–96.; Nishikura Annu Rev Biochem. 2010; 79: 321–349.; Thomas and Beal Bioessays. 2017 Apr;39(4)). All 3 ADARs contain a

dsRNA-binding domains (dsRBD), which can contact dsRNA substrates. Some ADAR1 also contains Z-DNA-binding domains. ADAR1 has been reported to expressed significantly in brain, lung, kidney, liver, and heart, etc., and may occur in two isoforms. In some embodiments, isoform p150 can be induced by interferon while isoform p110 can be constitutively expressed. In some embodiments, it can be beneficial to utilize p110 as it is reported to be ubiquitously and constitutively expressed. ADAR2 can be highly expressed, e.g. in the brain and lungs, and is reported to be exclusively localized to the nucleus. ADAR3 is reported to be catalytically inactive and expressed only in the brain. Potential differences in tissue expression can be taken into consideration when choosing a therapeutic target.

[00954] Use of oligonucleotides for RNA editing by ADAR has been reported. Among other things, the present disclosure recognizes that previously reported technologies generally suffer one or more disadvantages, such as low stability (e.g., oligonucleotides with natural RNA sugars), low editing efficiency, low editing specificity (e.g., a number of As are edited in a portion of a target nucleic acid substantially complementary to an oligonucleotide), specific structures in oligonucleotides for ADAR recognition/recruitment, exogenous proteins (e.g.,, those engineered to recognize oligonucleotides with specific structures and/or duplexes thereof (e.g.,, with target nucleic acids) for editing), etc. Additionally, previously reported technologies typically utilize stereorandom oligonucleotide compositions when oligonucleotides comprise one or more chiral linkage phosphorus of modified internucleotidic linkages.

[00955] For example, various reported oligonucleotides contain ADAR-recruiting domains. Merkle et al., Nat Biotechnol. 2019 Feb;37(2):133-138disclosed oligonucleotides comprising an imperfect 20-bp hairpin ADAR-recruiting domain that is an intramolecular stem loop to recruit endogenous human ADAR2 to edit endogenous transcript. Oligonucleotides reported in Mali et al., Nat Methods. 2019 Mar;16(3):239-242contain ADAR substrate GluR2 pre-messenger RNA sequences or MS2 hairpins in addition to specificity domains that hybridize to the target mRNA.

[00956] Certain reported editing approach utilizes exogenous or engineered proteins, e.g.,, those utilizing CRISPR/Cas9 system. For example, Komor et al. Nature 2016 volume533, pages420–424 disclosed deaminase coupled with CRISPR-Cas9 to create programmable DNA base editors. Since it engages in exogenous editing proteins, it requires the delivery of both the CRISPR/Cas9 system and the guide RNA.

[00957] Among other things, the present disclosure provides technologies comprising one or more features such as sugar modifications, base modifications, internucleotidic linkage modifications, control of stereochemistry, various patterns thereof, etc. to solve one or more or all disadvantaged suffered from prior adenosine editing technologies, for example, through providing chirally controlled oligonucleotide compositions of designed oligonucleotides described herein. For example, as demonstrated herein, ADAR-recruiting loops are optional and not required for provided technology.

[00958] As appreciated by those skilled in the art, one or more of such useful features may be utilized to improve oligonucleotides in prior technologies (e.g., those described in WO 2016097212, WO 2017220751, WO 2018041973, WO 2018134301, oligonucleotides and oligonucleotide compositions of each of which are

independently incorporated by reference). In some embodiments, the present disclosure provides improvements of prior technologies by apply one or more useful features described herein to prior reported oligonucleotide base sequences. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of previously reported oligonucleotides that may be useful for adenosine editing. In some embodiments, the present disclosure provides improvements of previously reported adenosine editing using stereorandom oligonucleotide compositions by performing such editing using chirally controlled oligonucleotide compositions.

[00959] As reported, ADAR proteins may have various isoforms. For example, ADAR1 has, among others, a reported p110 isoform and a reported p150 isoform. In some embodiments, it was observed that certain chirally controlled oligonucleotide compositions can provide high levels of adenosine modification (e.g., conversion of A to I) with multiple isoforms, in some embodiments, both p110 and p150 isoforms, while stereorandom compositions provide low levels of adenosine modification for one or more isoforms (e.g., p110). In some embodiments, chirally controlled oligonucleotide composition are particularly useful for adenosine modification in systems (e.g., cells, tissues, organs, organisms, subjects, etc.) expressing or comprising the p110 isoform of ADAR1, particularly those expressing or comprising high levels of the p110 isoform of ADAR1 relative to the p150 isoform, or those expressing no or low levels of ADAR1 p150.

[00960] In some embodiments, the present disclosure provides Cis-acting (CisA) oligonucleotide that do not require stem loop in the structure. In some embodiments, a provided oligonucleotide can form a dsRNA structure with a target mRNA through base pairing. In some embodiments, formed dsRNA structures (optionally with secondary mismatches) contain bulges that promote ADAR binding and therefore, can facilitate ADAR-mediated editing (e.g., deamination of a target adenosine). In some embodiments, oligonucleotides of the present disclosure are shorter than LSL oligonucleotides or CSL oligonucleotides, e.g., no more than or about 32 nt, no more than or about 31 nt, no more than or about 30 nt, no more than or about 29 nt, no more than or about 28 nt, no more than or about 27 nt, or no more than or about 26 nt in length, and can provide high editing efficiency.

Duplexing and Targeting Regions

[00961] In some embodiments, the present disclosure provides an oligonucleotide comprising:

a duplexing region; and

a targeting region;

wherein:

a duplexing region is capable of forming a duplex with a nucleic acid; and

a targeting region is capable of forming a duplex with a target nucleic acid comprising a target adenosine.

[00962] In some embodiments, a duplexing region is or comprises a first domain as described herein. In some embodiments, a targeting region is or comprises a second domain as described herein.

[00963] In some embodiments, a duplexing region is capable of forming a duplex with a nucleic acid, wherein the nucleic acid is not a target nucleic acid. In some embodiments, a duplexing region forms a duplex with a target nucleic acid. In some embodiments, a duplexing region forms a duplex with a nucleic acid expressed in a system, e.g., a cell. In some embodiments, a duplexing region forms a duplex with an exogenous nucleic acid, e.g., an oligonucleotide. In some embodiments, a duplexing region forms a duplex with a nucleic acid which is or comprises a RNA portion. In some embodiments, a duplex formed can be recognized by a polypeptide such as an ADAR polypeptide, e.g., ADAR1 (p110 or p150 or both), ADAR2, etc. In some embodiments, a duplex formed can recruit a polypeptide such as an ADAR polypeptide, e.g., ADAR1 (p110 or p150 or both), ADAR2, etc. In some embodiments, a duplex formed recruit ADAR1. In some embodiments, a duplex formed recruit ADAR1 p110. In some embodiments, a duplex formed recruit ADAR1 p150. In some embodiments, a duplex formed recruit ADAR2. In some embodiments, a duplex formed recruit ADAR1 p110 and p150. In some embodiments, a duplex formed recruit ADAR1 and ADAR2. In some embodiments, a duplex formed recruit ADAR1 p110, ADAR p150 and/or ADAR2. In some embodiments, a duplex formed recruit ADAR1 p110 and p150 and ADAR2.

[00964] In some embodiments, a duplexing region forms a duplex with an oligonucleotide (which oligonucleotide may be referred to as "a duplexing oligonucleotide"). In some embodiments, a duplexing oligonucleotide comprises one or more modified nucleobases, modified sugars and/or modified internucleotidic linkages. In some embodiments, an duplexing oligonucleotide comprises a duplex-forming region that is complementary to a duplexing region. As those skilled in the art appreciate, in many instances, perfect complementary is not required and one or more wobbles, bulges, mismatches, etc. may be well tolerated. For example, ADAR proteins have been reported to bind to and/or utilize as substrates both perfectly and imperfectly complementary duplexes.

[00965] Duplexing regions and/or duplexing-forming regions can be of various lengths. In some embodiments, they are at least 10 (e.g., about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, about 10-20, 10-25, 10-30, 10-40, 10-50, 10-100, 14-20, 14-25, 14-30, 14-40, 14-50, 14-100, 15-20, 15-25, 15-30, 15-40, 15-50, 15-100, 16-20, 16-25, 16-30, 16-40, 16-50, 16-100, 17-20, 17-25, 17-30, 17-40, 17-50, 17-100, 18-20, 18-25, 18-30, 18-40, 18-50, 18-100, 19-20, 19-25, 19-30, 19-40, 19-50, 19-100, 20-25, 20-30, 20-40, 20-50, 20-100, etc.) nucleosides in length. In some embodiments, a length is about or at least about 10 nucleosides in length. In some embodiments, a length is about or at least about 11 nucleosides in length. In some embodiments, a length is about or at least about 12 nucleosides in length. In some embodiments, a length is about or at least about 13 nucleosides in length. In some embodiments, a length is about or at least about 14 nucleosides in length. In some embodiments, a length is about or at least about 15 nucleosides in length. In some embodiments, a length is about or at least about 16 nucleosides in length. In some embodiments, a length is about or at least about 17 nucleosides in length. In some embodiments, a length is about or at least about 18 nucleosides in length. In some embodiments, a length is about or at least about 19 nucleosides in length. In some embodiments, a length is about or at least about 20

nucleosides in length.

[00966] In some embodiments, a duplexing oligonucleotide consists of or consists essentially of a duplex-forming region. In some embodiments, a duplexing oligonucleotide further comprises one or more additional regions in addition to a duplex-forming region. In some embodiments, a duplexing oligonucleotide comprises a stem-loop region (e.g., as described in Figure 35). In some embodiments, a duplexing oligonucleotide comprises or consists of a duplex-forming region and a stem-loop region. In some embodiments, a stem region is about or at least about 2, 3, 4, 5, 6, 7, 8, 9, or 10 (e.g., about or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, about 4-10, 4-15, 4-20, 4-25, 4-30, 4-40, 4-50, 5-10, 5-15, 5-20, 5-25, 5-30, 5-40, 5-50, 6-10, 6-15, 6-20, 6-25, 6-30, 6-40, 6-50, 7-10, 7-15, 7-20, 7-25, 7-30, 7-40, 7-50, 8-10, 8-15, 8-20, 8-25, 8-30, 8-40, 8-50, 9-10, 9-15, 9-20, 9-25, 9-30, 9-40, 9-50, 10-15, 10-25, 10-30, 10-40, 10-50, 10-100, etc.) nucleobase in length. In some embodiments, it is about or at least about 5 nucleobases in length. In some embodiments, it is about or at least about 6 nucleobases in length. In some embodiments, it is about or at least about 7 nucleobases in length. In some embodiments, it is about or at least about 8 nucleobases in length. In some embodiments, it is about or at least about 9 nucleobases in length. In some embodiments, it is about or at least about 10 nucleobases in length.

[00967] In some embodiments, one or more additional regions may promote, encourage, facilitate and/or contribute recruitment of and/or recognition by and/or interaction with a polypeptide, e.g., ADAR1 (p110 and/or p150) and/or ADAR2. In some embodiments, for duplexing oligonucleotides comprising one or more additional regions, shorter duplex-forming regions may be utilized compared to absence of such additional regions.

[00968] In some embodiments, a duplex structure formed by a duplex region and a duplexing oligonucleotide can recruit a polypeptide, e.g., ADAR1 (p110 and/or p150) and/or ADAR2. In some embodiments, a duplex structure is or comprises a recruiting portion as described in WO 2016/097212.

[00969] In some embodiments, a duplexing oligonucleotide comprises one or more sugar, nucleobase, and/or internucleotidic linkage modifications as described herein. In some embodiments, a duplexing oligonucleotide comprises one or more sugar modification. In some embodiments, a majority, as described herein, of, or all of, the sugars in a duplexing oligonucleotide is a modified sugar. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, each modified sugar is independently a 2'-modified sugar. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is not hydrogen. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE modified sugar.

In some embodiments, each 2'-OR modified sugar is independently a 2'-F modified sugar. In some embodiments, a duplexing oligonucleotide comprises one or more modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages. In some embodiments, a majority, as described herein, of or all of internucleotidic linkages of a duplexing oligonucleotide are independently modified internucleotidic linkages. In some embodiments, each internucleotidic linkage of a duplexing oligonucleotide is independently a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is n001. In some embodiments, each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, a phosphorothioate internucleotidic linkage is not chirally controlled. In some embodiments, a majority, as described herein, of, or all of, chirally controlled phosphorothioate internucleotidic linkages are independently *S*p. In some embodiments, all phosphorothioate internucleotidic linkages are *S*p. In some embodiments, a duplexing oligonucleotide comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 or more) natural phosphate linkages. In some embodiments, when an oligonucleotide comprises one or more natural phosphate linkages, one or several internucleotidic linkages at the 5' and/or 3' end are independently modified internucleotidic linkages as described herein. In some embodiments, several internucleotidic linkages at both the 5' and 3' ends are independently modified internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 3' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, increasing the number of modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, etc., can increase editing efficiency, e.g., when more natural DNA/RNA sugars, 2'-F modified sugars, etc., are bonded to modified internucleotidic linkages such as phosphorothioate internucleotidic linkages.

[00970] In some embodiments, a duplexing region comprises one or more sugar, nucleobase and/or internucleotidic linkage modifications as described herein. In some embodiments, a duplexing region comprises one or more (e.g., 1-30, 1-20, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, etc.) modified sugars as described herein. In some embodiments, a majority, as described herein, of or all of sugars in a duplexing region are each independently a modified sugar as described herein. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, each modified sugar is independently a 2'-modified sugar. In some embodiments, each modified sugar is independently selected from

a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is not hydrogen. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe or a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-F modified sugar. In some embodiments, about 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more of sugars in a duplexing region are each independently a 2'-F modified sugar. In some embodiments, as described herein, one or more sugars at an end of an oligonucleotide is independently a modified sugar. In some embodiments, as described herein, one or more sugars at an end of an oligonucleotide is independently a bicyclic sugar or a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, as described herein, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at an end of an oligonucleotide are each independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at both ends of an oligonucleotide are each independently a modified sugar; for example, in some oligonucleotides, 3 or more sugars at the 5' end are 2'-OMe modified sugars, and 4 or more sugars at the 3' end are 2'-OMe modified sugars. In some embodiments, a duplexing region comprises one or more (e.g., 1-30, 1-20, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, etc.) modified internucleotidic linkages as described herein. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' and/or 3' ends of an oligonucleotide are each independently a modified internucleotidic linkage, e.g., in some embodiments, each independently selected from a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, a phosphoryl guanidine internucleotidic linkage, n001 and a phosphorothioate internucleotidic linkage. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' end of an oligonucleotide are each independently a modified internucleotidic linkage, and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 3' end of an oligonucleotide are each independently a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is n001. In some embodiments, each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some

embodiments, a phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, a phosphorothioate internucleotidic linkage is not chirally controlled. In some embodiments, a majority, as described herein, of, or all of, chirally controlled phosphorothioate internucleotidic linkages are independently *S*p. In some embodiments, all phosphorothioate internucleotidic linkages are *S*p. In some embodiments, chiral modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are not chirally controlled. In some embodiments, a duplexing region comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 or more) natural phosphate linkages. In some embodiments, when an oligonucleotide comprises one or more natural phosphate linkages, one or several internucleotidic linkages at the 5' and/or 3' end are independently modified internucleotidic linkages as described herein. In some embodiments, several internucleotidic linkages at both the 5' and 3' ends are independently modified internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 3' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, incorporation of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) natural phosphate linkages at duplexing regions increase editing efficiency. In some embodiments, a majority of internucleotidic linkages (e.g., 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) in a duplexing region are independently natural phosphate linkages. In some embodiments, except the one or more natural phosphate linkages at an end of an oligonucleotide (if any), each other internucleotidic linkage in a duplexing region is independently a natural phosphate linkage.

[00971] In some embodiments, a targeting region is or comprises an editing region as described herein. In some embodiments, a targeting region comprises 5'-$N_1N_0N_{-1}$-3' as described herein.

[00972] In some embodiments, a targeting region comprises one or more sugar, nucleobase and/or internucleotidic linkage modifications as described herein. In some embodiments, a targeting region comprises one or more (e.g., 1-30, 1-20, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, etc.) modified sugars as described herein. In some embodiments, a majority, as described herein, of or all of sugars in a targeting region are each independently a modified sugar as described herein. In some embodiments, a modified sugar is a 2'-modified sugar. In some embodiments, each modified sugar is independently a 2'-modified sugar. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is not hydrogen. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar, a bicyclic sugar, or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each modified sugar is independently selected from a 2'-F modified sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each 2'-OR modified sugar is independently a 2'-

OMe or a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-OMe modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-MOE modified sugar. In some embodiments, each 2'-OR modified sugar is independently a 2'-F modified sugar. In some embodiments, about 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more of sugars in a targeting region are each independently a bicyclic sugar or a 2'-OR modified sugar wherein R is not hydrogen. In some embodiments, about 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more of sugars in a targeting region are each independently a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, about 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more of sugars in a targeting region are each independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in a targeting region except the sugars in an editing region is independently a modified sugar as described herein. In some embodiments, each sugar in a targeting region except the sugars in an editing region is independently a bicyclic sugar or a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a targeting region except the sugars in an editing region is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, each sugar in a targeting region except the sugars in an editing region is independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, each sugar in a targeting region except the sugars in an editing region is independently a 2'-OMe modified sugar. In some embodiments, an editing region comprises or consists of three nucleosides wherein a nucleoside opposite to a target adenosine is in the middle of the three. In some embodiments, an editing region consists of three nucleosides wherein a nucleoside opposite to a target adenosine is in the middle of the three. In some embodiments, an editing region comprising or consisting of 5'-$N_1N_0N_{-1}$-3'. In some embodiments, as described herein, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at an end of an oligonucleotide is independently a modified sugar. In some embodiments, as described herein, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at an end of an oligonucleotide is independently a bicyclic sugar or a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, as described herein, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at an end of an oligonucleotide are each independently a 2'-OR modified sugar wherein R is C_{1-6} aliphatic. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) sugars at both ends of an oligonucleotide are each independently a modified sugar; for example, in some oligonucleotides, 3 or more sugars at the 5' end are 2'-OMe modified sugars, and 4 or more sugars at the 3' end are 2'-OMe modified sugars. In some embodiments, a targeting region comprises one or more (e.g., 1-30, 1-20, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more, etc.) modified internucleotidic linkages as described herein. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' and/or 3' ends of an oligonucleotide are each

independently a modified internucleotidic linkage, e.g., in some embodiments, each independently selected from a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, a phosphoryl guanidine internucleotidic linkage, n001 and a phosphorothioate internucleotidic linkage. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' end of an oligonucleotide are each independently a modified internucleotidic linkage, and one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 3' end of an oligonucleotide are each independently a modified internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is n001. In some embodiments, each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a phosphorothioate internucleotidic linkage is chirally controlled. In some embodiments, a phosphorothioate internucleotidic linkage is not chirally controlled. In some embodiments, a majority, as described herein, of, or all of, chirally controlled phosphorothioate internucleotidic linkages are independently *S*p. In some embodiments, all phosphorothioate internucleotidic linkages are *S*p. In some embodiments, chiral modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are not chirally controlled. In some embodiments, a targeting region comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 or more) natural phosphate linkages. In some embodiments, when an oligonucleotide comprises one or more natural phosphate linkages, one or several internucleotidic linkages at the 5' and/or 3' end are independently modified internucleotidic linkages as described herein. In some embodiments, several internucleotidic linkages at both the 5' and 3' ends are independently modified internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 5' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) internucleotidic linkages at the 3' end are modified internucleotidic linkages as described herein, e.g., phosphorothioate internucleotidic linkages. In some embodiments, incorporation of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 2-20, 2-10, 2-5, 3-5, etc.) natural phosphate linkages at targeting regions increase editing efficiency. In some embodiments, a majority of internucleotidic linkages (e.g., 50%-100%, 60%-100%, 70%-100%, 50%-90%, 50%-80%, 60%-90%, 60%-80%, 70%-90%, 70%-80%, or about or at least about 60%, 70%, 75%, 80%, 85%, 90%, 95% or more) in a targeting region are independently natural phosphate linkages. In some embodiments, except the one or more natural phosphate linkages at an end of an oligonucleotide (if any), each other internucleotidic linkage in a targeting region is independently a natural phosphate linkage.

[00973] In some embodiments, a targeting region is complementary to a sequence in a target nucleic acid.

In some embodiments, a nucleic acid is or comprise RNA. In some embodiments, a nucleic acid is RNA. In some embodiments, a sequence in a target nucleic acid to which a target region is complementary to comprises a target adenosine. As those skilled in the art appreciate, full complementarity in many instances are not required, and one or more wobbles, bulges, mismatches, etc. may be present.

[00974] Targeting regions can be of various lengths. In some embodiments, a targeting region is at least 10 (e.g., about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more, about 10-20, 10-25, 10-30, 10-40, 10-50, 10-100, 14-20, 14-25, 14-30, 14-40, 14-50, 14-100, 15-20, 15-25, 15-30, 15-40, 15-50, 15-100, 16-20, 16-25, 16-30, 16-40, 16-50, 16-100, 17-20, 17-25, 17-30, 17-40, 17-50, 17-100, 18-20, 18-25, 18-30, 18-40, 18-50, 18-100, 19-20, 19-25, 19-30, 19-40, 19-50, 19-100, 20-25, 20-30, 20-40, 20-50, 20-100, etc.) nucleosides in length. In some embodiments, a length is about or at least about 10 nucleosides in length. In some embodiments, a length is about or at least about 11 nucleosides in length. In some embodiments, a length is about or at least about 12 nucleosides in length. In some embodiments, a length is about or at least about 13 nucleosides in length. In some embodiments, a length is about or at least about 14 nucleosides in length. In some embodiments, a length is about or at least about 15 nucleosides in length. In some embodiments, a length is about or at least about 16 nucleosides in length. In some embodiments, a length is about or at least about 17 nucleosides in length. In some embodiments, a length is about or at least about 18 nucleosides in length. In some embodiments, a length is about or at least about 19 nucleosides in length. In some embodiments, a length is about or at least about 20 nucleosides in length. In some embodiments, a length is about or at least about 21 nucleosides in length. In some embodiments, a length is about or at least about 22 nucleosides in length. In some embodiments, a length is about or at least about 23 nucleosides in length. In some embodiments, a length is about or at least about 24 nucleosides in length. In some embodiments, a length is about or at least about 25 nucleosides in length.

[00975] In some embodiments, an oligonucleotide comprises a targeting region and a duplexing region, wherein the targeting region is at the 3' side of the duplexing region. In some embodiments, an oligonucleotide comprises a targeting region and a duplexing region, wherein the targeting region is at the 5' side of the duplexing region. In some embodiments, an oligonucleotide consists of a targeting region and a duplexing region, wherein the targeting region is at the 3' side of the duplexing region. In some embodiments, an oligonucleotide consists of a targeting region and a duplexing region, wherein the targeting region is at the 5' side of the duplexing region. In some embodiments, an oligonucleotide comprise a targeting region, a duplexing region and a linker region between the target and duplexing regions. In some embodiments, a linker region comprises or is an oligonucleotide moiety.

[00976] In some embodiments, oligonucleotides comprising duplexing and targeting regions form complexes including duplexes with other nucleic acids e.g., duplexing oligonucleotides. In some embodiments, the present disclosure provides duplexes comprising oligonucleotides comprising duplexing and targeting regions and nucleic acids that form duplexes with duplexing regions. In some embodiments, the present disclosure provides duplexes comprising oligonucleotides comprising duplexing and targeting regions

and duplexing oligonucleotides. In some embodiments, chirally controlled oligonucleotide compositions of oligonucleotides comprising duplexing and targeting regions are utilized (e.g., WV-42707). In some embodiments, non-chirally controlled oligonucleotide compositions of oligonucleotides comprising duplexing and targeting regions are utilized. In some embodiments, chirally controlled oligonucleotide compositions of duplexing oligonucleotides are utilized (e.g., WV-42724). In some embodiments, non-chirally controlled oligonucleotide compositions of duplexing oligonucleotides are utilized (e.g., WV-42721).

[00977] In some embodiments, duplexes are formed before administration. In some embodiments, oligonucleotides comprising duplexing and targeting regions and nucleic acids forming duplexes therewith (which may be referred to as "duplexing nucleic acids") are administered separately. In some embodiments, oligonucleotides comprising duplexing and targeting regions are administered prior to, concurrently with (either in a single or multiple compositions) or subsequently to duplexing nucleic acids (e.g., various duplexing oligonucleotides described herein). In some embodiments, duplexing nucleic acids are present in and/or can be expressed in cells and thus may not need to be administered directly.

[00978] Certain oligonucleotides comprising duplexing and targeting regions and/or duplexing nucleic acids (e.g., duplexing oligonucleotides) and/or uses are described in Figure 33, Figure 34 and Figure 35, etc. as examples.

[00979] In some embodiments, a target nucleic acid is or comprises RNA. In some embodiments, a target nucleic acid is or comprises mRNA. In some embodiments, a target adenosine in a target nucleic acid is edited to I.

Production of Oligonucleotides and Compositions

[00980] Various methods can be utilized for production of oligonucleotides and compositions and can be utilized in accordance with the present disclosure. For example, traditional phosphoramidite chemistry (e.g., phosphoramidites comprising $-CH_2CH_2CN$ and $-N(i\text{-}Pr)_2$) can be utilized to prepare stereorandom oligonucleotides and compositions, and certain reagents and chirally controlled technologies can be utilized to prepare chirally controlled oligonucleotide compositions, e.g., as described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the reagents and methods of each of which is incorporated herein by reference.

[00981] In some embodiments, chirally controlled/stereoselective preparation of oligonucleotides and compositions thereof comprise utilization of a chiral auxiliary, e.g., as part of monomers, dimers (e.g., chirally pure dimers from separation), monomeric phosphoramidites, dimeric phosphoramidites (e.g., chirally pure dimers from separation), etc. Examples of such chiral auxiliary reagents, monomers, dimers, and phosphoramidites are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US

9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the chiral auxiliary reagents, monomers, dimers, and phosphoramidites of each of which are independently incorporated herein by reference. In some embodiments, a chiral auxiliary is a chiral auxiliary described in any of: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the chiral auxiliaries of each of which are independently incorporated herein by reference.

[00982] In some embodiments, chirally controlled preparation technologies, including oligonucleotide synthesis cycles, reagents and conditions are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, and/WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the oligonucleotide synthesis methods, cycles, reagents and conditions of each of which are independently incorporated herein by reference.

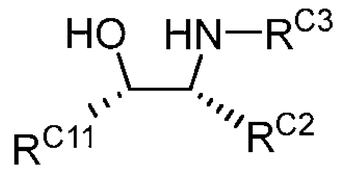
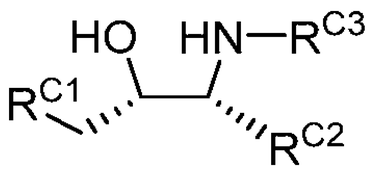
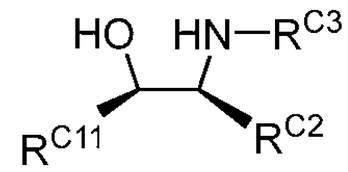
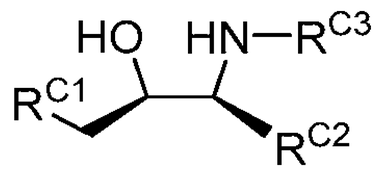
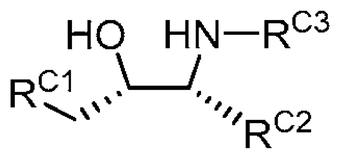
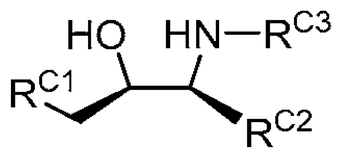
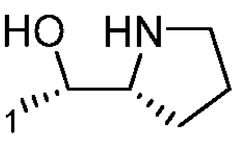
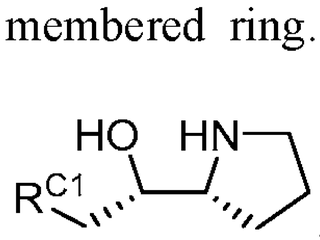
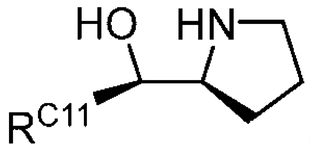
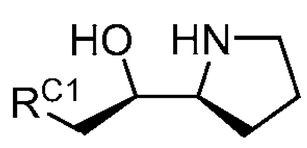
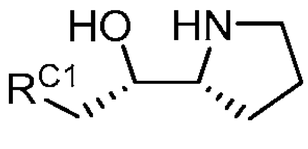
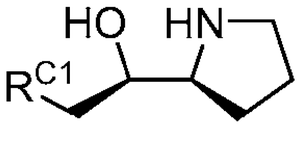
[00983] Once synthesized, provided oligonucleotides and compositions are typically further purified. Suitable purification technologies are widely known and practiced by those skilled in the art, including but not limited to those described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the purification technologies of each of which are independently incorporated herein by reference.

[00984] In some embodiments, a cycle comprises or consists of coupling, capping, modification and deblocking. In some embodiments, a cycle comprises or consists of coupling, capping, modification, capping and deblocking. These steps are typically performed in the order they are listed, but in some embodiments, as appreciated by those skilled in the art, the order of certain steps, e.g., capping and modification, may be altered. If desired, one or more steps may be repeated to improve conversion, yield and/or purity as those skilled in the art often perform in syntheses. For example, in some embodiments, coupling may be repeated; in some embodiments, modification (e.g., oxidation to install =O, sulfurization to install =S, etc.) may be repeated; in some embodiments, coupling is repeated after modification which can convert a P(III) linkage to a P(V) linkage which can be more stable under certain circumstances, and coupling is routinely followed by modification to convert newly formed P(III) linkages to P(V) linkages. In some embodiments, when steps are repeated,

different conditions may be employed (e.g., concentration, temperature, reagent, time, etc.).

[00985] Technologies for formulating provided oligonucleotides and/or preparing pharmaceutical compositions, e.g., for administration to subjects via various routes, are readily available in the art and can be utilized in accordance with the present disclosure, e.g., those described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, or WO 2018/237194 and references cited therein.

[00986] Technologies for formulating provided oligonucleotides and/or preparing pharmaceutical compositions, e.g., for administration to subjects via various routes, are readily available in the art and can be utilized in accordance with the present disclosure, e.g., those described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, or WO 2018/237194 and references cited therein.

[00987] In some embodiments, a useful chiral auxiliary has the structure of  ,  ,  , or  , or a salt thereof, wherein R^{C11} is $-L^{C1}-R^{C1}$, L^{C1} is optionally substituted $-CH_2-$, R^{C1} is R, $-Si(R)_3$, $-SO_2R$ or an electron-withdrawing group, and R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-10 membered saturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms. In some embodiments, a useful chiral auxiliary has the structure of  or  , wherein R^{C1} is R, $-Si(R)_3$ or $-SO_2R$, and R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms. is a formed ring is an optionally substituted 5-membered ring. In some embodiments, a useful chiral auxiliary has the structure of  ,  ,  , or  , or a salt thereof. In some embodiments, a useful chiral auxiliary has the structure of  or  . In some embodiments, a useful chiral auxiliary is a DPSE chiral auxiliary. In some embodiments, purity or stereochemical purity of a chiral auxiliary is at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, it is at least 85%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%. In some embodiments, it is at least

96%. In some embodiments, it is at least 97%. In some embodiments, it is at least 98%. In some embodiments, it is at least 99%.

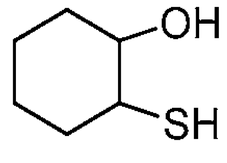
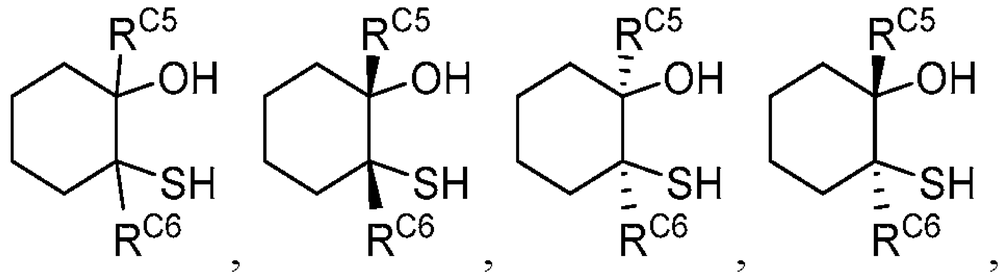
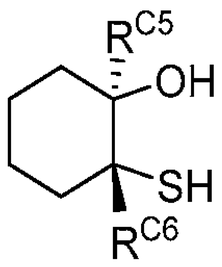
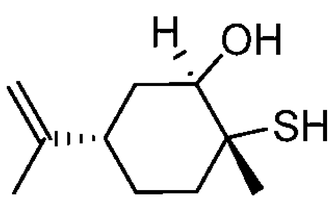
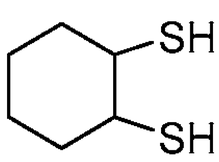
[00988] In some embodiments, L^{C1} is $-CH_2-$. In some embodiments, L^{C1} is substituted $-CH_2-$. In some embodiments, L^{C1} is mono-substituted $-CH_2-$.

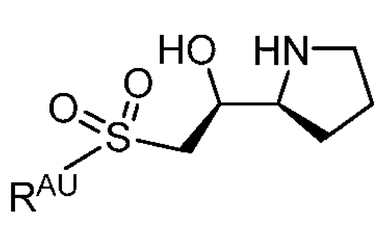
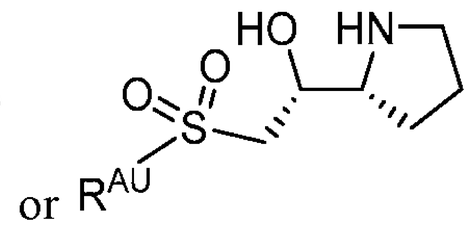
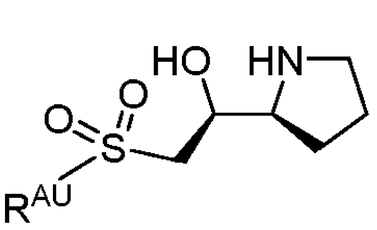
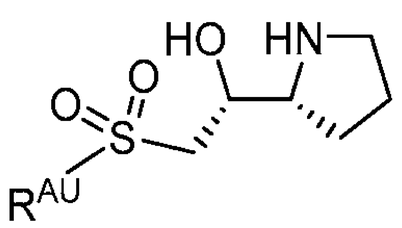
[00989] In some embodiments, R^{C1} is R. In some embodiments, R^{C1} is optionally substituted phenyl. In some embodiments, R^{C1} is $-SiR_3$. In some embodiments, R^{C1} is $-SiPh_2Me$. In some embodiments, R^{C1} is $-SO_2R$. In some embodiments, R is not hydrogen. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is t-butyl.

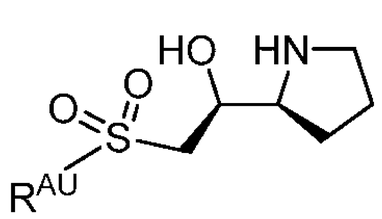
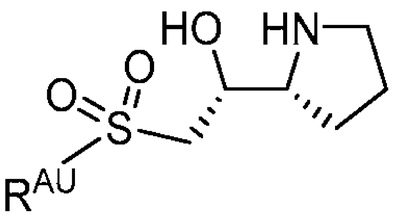
[00990] In some embodiments, R^{C1} is an electron-withdrawing group, such as $-C(O)R$, $-OP(O)(OR)_2$, $-OP(O)(R)_2$, $-P(O)(R)_2$, $-S(O)R$, $-S(O)_2R$, etc. In some embodiments, chiral auxiliaries comprising electron-withdrawing group R^{C1} groups are particularly useful for preparing chirally controlled non-negatively charged internucleotidic linkages and/or chirally controlled internucleotidic linkages bonded to natural RNA sugar.

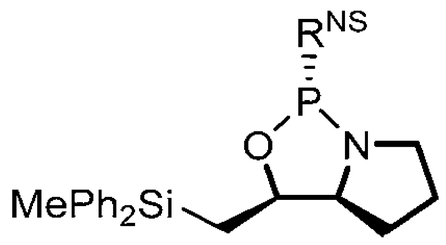
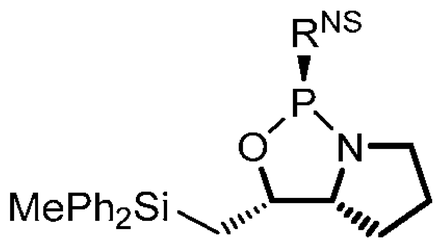
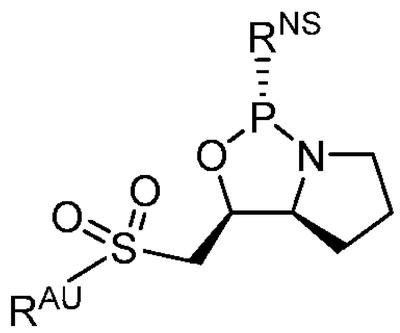
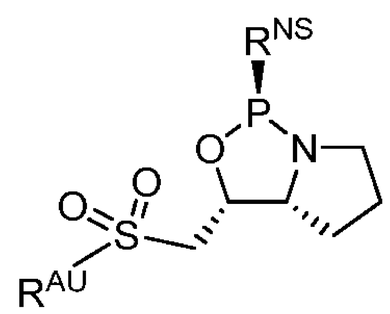
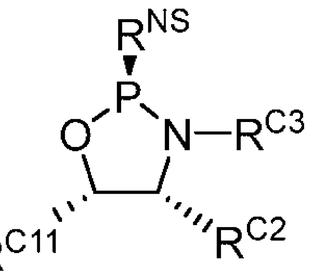
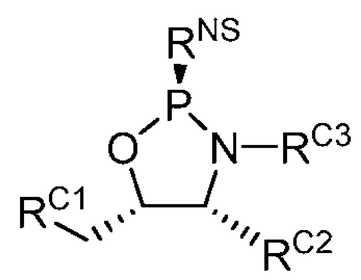
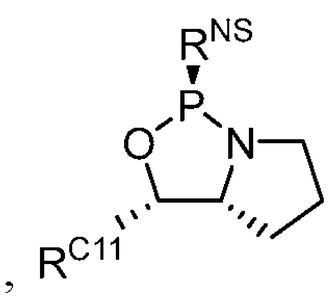
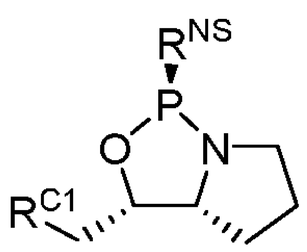
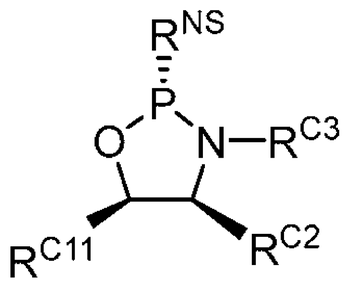
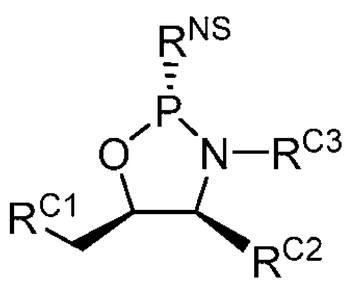
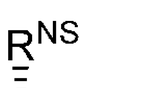
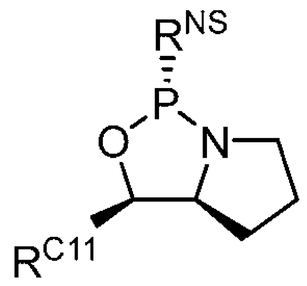
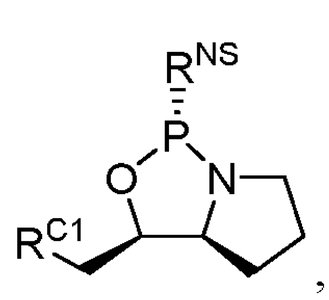
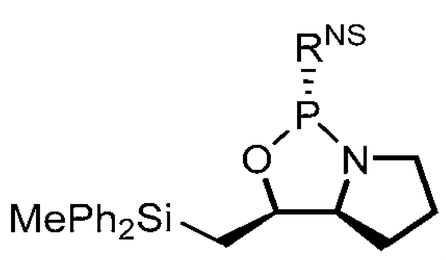
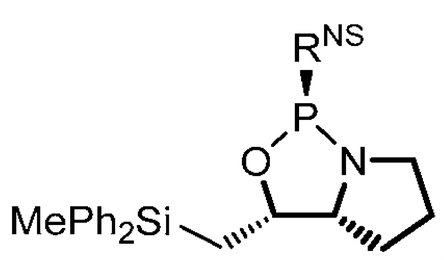
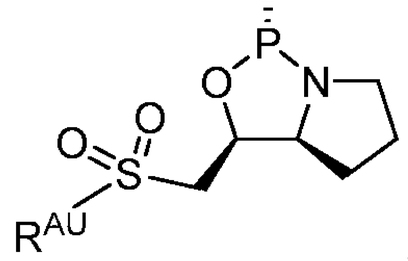
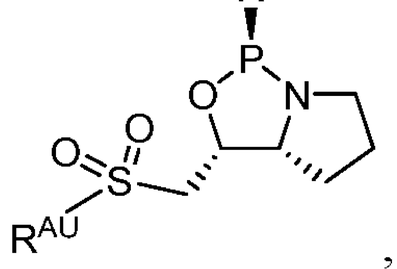
[00991] In some embodiments, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered saturated ring having no heteroatoms in addition to the nitrogen atom. In some embodiments, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 5-membered saturated ring having no heteroatoms in addition to the nitrogen atom.

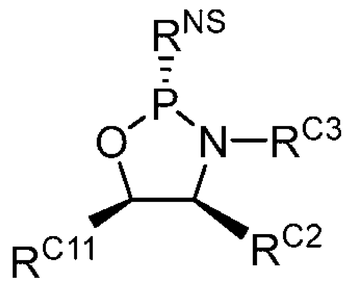
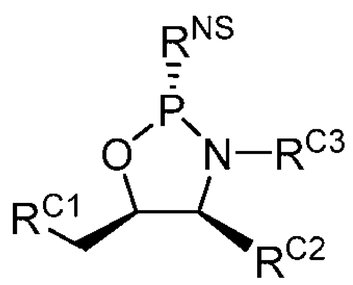
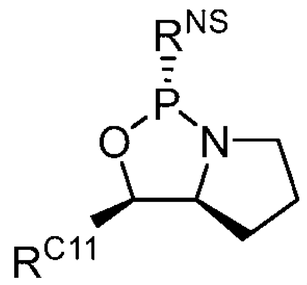
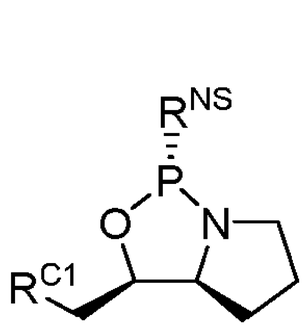
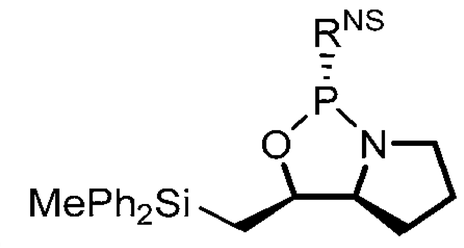
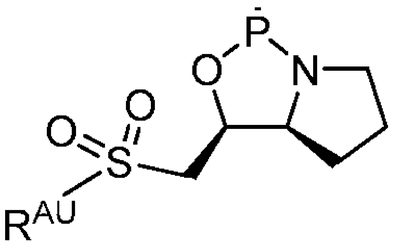
[00992] In some embodiments, a compound has the structure of $H-X^C-C(R^{C5})_2-C(R^{C6})_2-SH$ or a salt thereof, wherein X^C is O or S, and each of R^{C5} and R^{C6} is independently R as described herein. In some embodiments, such a compound is useful for preparing a monomer. In some embodiments, such a compound is useful as a chiral auxiliary. In some embodiments, such a compound is particularly useful for preparing monomer which when utilized in oligonucleotide synthesis form bonds between their nitrogen atoms with linkage phosphorus (e.g., monomers comprising sm01, sm18, etc.). In some embodiments, X^C is O. In some embodiments, X^C is S. In some embodiments, one R^{C5} is $-H$. In some embodiments, one R^{C6} is $-H$. In some embodiments, a compound has the structure of $H-X^C-CHR^{C5}-CHR^{C6}-SH$ or a salt thereof. In some embodiments, R^{C5} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{C5} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{C5} is methyl. In some embodiments, R^{C6} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{C6} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{C6} is methyl. In some embodiments, a compound is $HOCH(CH_3)CH(CH_3)SH$. In some embodiments, a compound is $HSCH(CH_3)CH(CH_3)SH$. In some embodiments, one R^{C5} is not hydrogen. In some embodiments, one R^{C6} is not hydrogen. In some embodiments, one R^{C5} and one R^{C6} are taken together with their intervening atoms to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 5-10, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) membered monocyclic, bicyclic or polycyclic ring having 0-5 heteroatoms. In some embodiments, a formed ring is monocyclic. In some embodiments, one R^{C5} and one R^{C6} are taken together with their intervening atoms to form an optionally substituted 4-8, 4-7, 5-8, 5-7, 4, 5, 6, 7, or 8-membered monocyclic

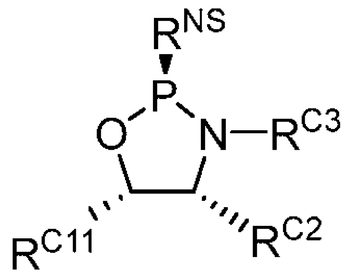
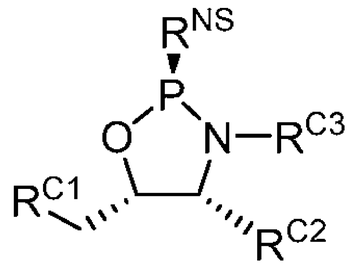
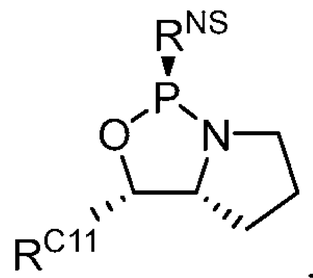
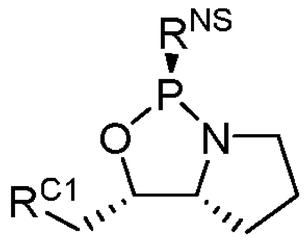
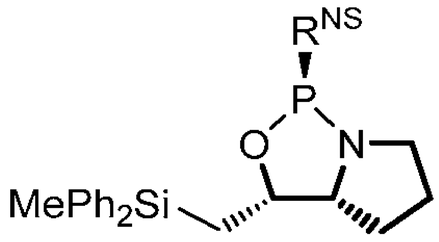
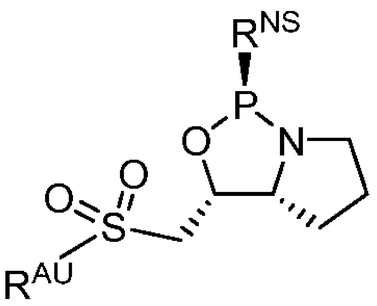
ring. In some embodiments, a formed ring is a saturated cycloalkyl ring. In some embodiments, a formed ring is a cyclohexyl ring. In some embodiments, a formed ring is bicyclic. In some embodiments, a formed ring contain no heteroatom ring atoms. In some embodiments, each monocyclic ring unit is independently 3-10 membered, and/or is independently saturated, partially unsaturated or aromatic and has 0-5 heteroatoms. In some embodiments, a compound is  or a salt thereof, wherein the cyclohexyl ring is optionally substituted. In some embodiments, a compound is  , or  , or a salt thereof, wherein the cyclohexyl ring is optionally substituted. In some embodiments, a substituent is C_{1-6} aliphatic, e.g., $-C(CH_3)=CH_2$. For example, in some embodiments, a compound is  . In some embodiments, a compound is  or a salt thereof, wherein the cyclohexyl ring is optionally substituted.

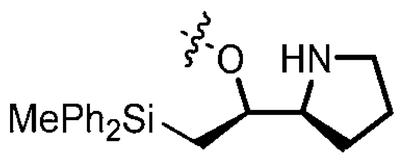
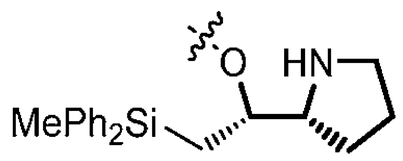
[00993] In some embodiments, methods for preparing oligonucleotides and/or compositions comprise using a chiral auxiliary described herein, e.g., for constructing one or more chirally controlled internucleotidic linkages. In some embodiments, one or more chirally controlled internucleotidic linkages are independently constructed using a DPSE chiral auxiliary. In some embodiments, each chirally controlled phosphorothioate internucleotidic linkage is independently constructed using a DPSE chiral auxiliary. In some embodiments, one or more chirally controlled internucleotidic linkages are independently constructed using  or  , or a salt thereof, wherein R^{AU} is as described herein. In some embodiments, each chirally controlled non-negatively charged internucleotidic linkage (e.g., n001) is independently constructed using  or  , or a salt thereof. In some embodiments, each chirally controlled internucleotidic linkage is independently constructed using

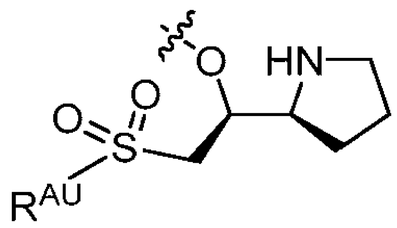
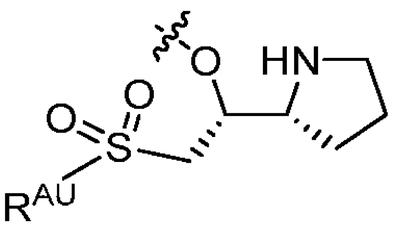
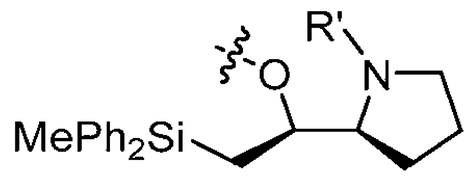
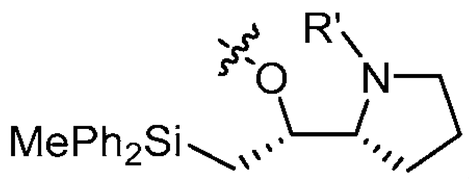
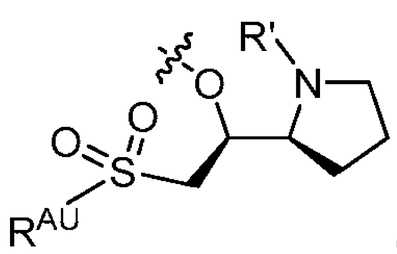
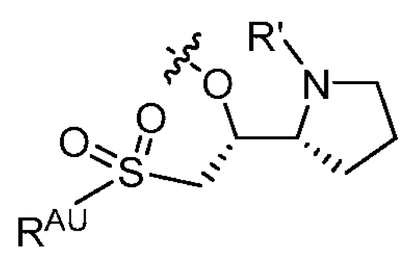
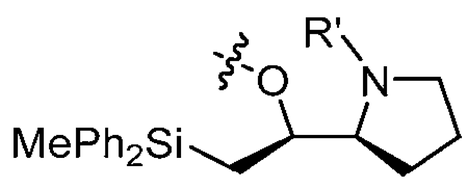
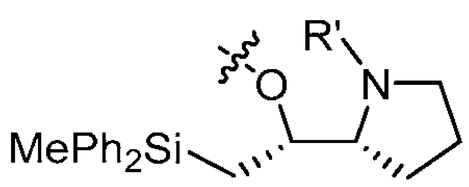
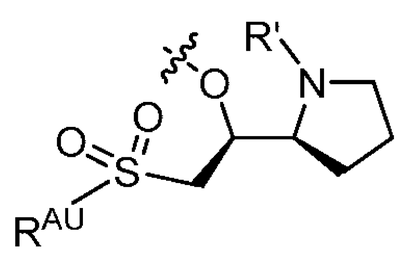
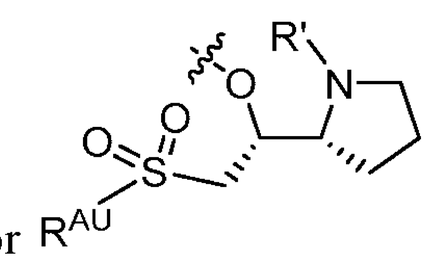
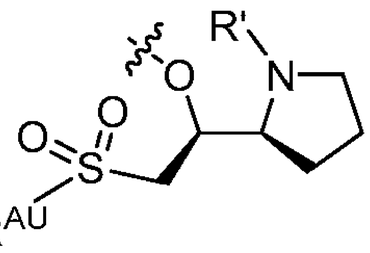
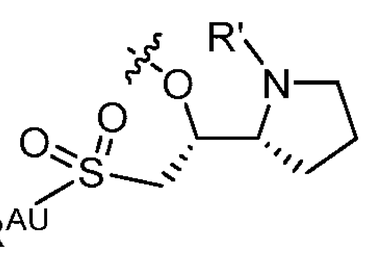



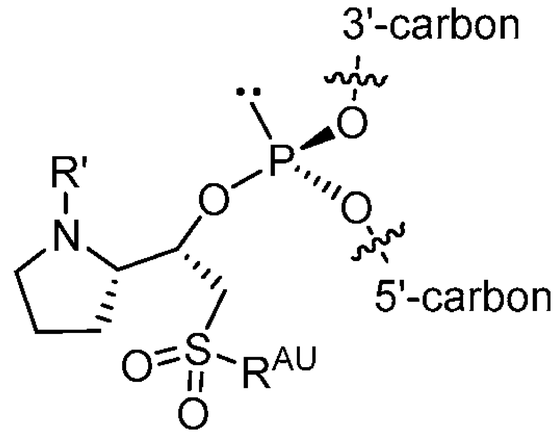
, or a salt thereof. In some embodiments, R^{AU} is optionally substituted C_{1-20}, C_{1-10}, C_{1-6}, C_{1-5}, or C_{1-4} aliphatic. In some embodiments, R^{AU} is optionally substituted C_{1-20}, C_{1-10}, C_{1-6}, C_{1-5}, or C_{1-4} alkyl. In some embodiments, R^{AU} is optionally substituted aryl. In some embodiments, R^{AU} is phenyl. In some embodiments, one or more chirally controlled internucleotidic linkages are constructed using a PSM chiral auxiliary. In some embodiments, each chirally controlled non-negatively charged internucleotidic linkage (e.g., n001) is independently constructed using a PSM chiral auxiliary. In some embodiments, each chirally controlled internucleotidic linkages is independently constructed using a PSM chiral auxiliary. As appreciated by those skilled in the art, a chiral auxiliary is often utilized in a phosphoramidite (e.g.,  or  (DPSE phosphoramidites),  or  (wherein R^{AU} is independently as described herein; when R^{AU} is −Ph, PSM phosphoramidites), wherein R^{NS} is an optionally substituted/protected nucleoside (e.g., optionally protected for oligonucleotide synthesis), or a salt thereof, etc.) for oligonucleotide preparation. In some embodiments, a phosphoramidite is a compound having the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , or salt thereof, wherein each variable is independently as described herein. In some embodiments, R^{AU} is optionally substituted phenyl. In some embodiments, R^{AU} is phenyl. In some embodiments, R^{NS} is an optionally substituted or protected nucleoside comprising hypoxanthine. In some embodiments, R^{NS} comprises optionally

substituted or protected hypoxanthine. In some embodiments, R^{NS} is optionally substituted or protected inosine. In some embodiments, R^{NS} is optionally substituted or protected deoxyinosine. In some embodiments, R^{NS} is optionally substituted or protected 2'-F inosine (2'-OH replaced with 2'-F). In some embodiments, R^{NS} is optionally substituted or protected 2'-OR modified inosine (2'-OH replaced with a 2'-OR modification as described herein (e.g., 2'-OMe, 2'-MOE, etc.)). In some embodiments, hypoxanthine is O^6 protected. In some embodiments, hypoxanthine is O^6 protected with $-L-Si(R)_3$, wherein L is optionally substituted $-CH_2-CH_2-$, and each R is independently as described herein and not $-H$. In some embodiments, each R is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, each R is independently optionally substituted C_{1-6} alkyl. In some embodiments, $-L-Si(R)_3$ is $-CH_2CH_2Si(Me)_3$. In some embodiments, compounds comprising O^6 protected hypoxanthine (e.g., with $-CH_2CH_2Si(Me)_3$) have higher solubility than corresponding O^6 unprotected compounds and may provide various benefits and advantages when utilized for oligonucleotide synthesis in accordance with the present disclosure. In some embodiments, in a compound having the structure of  ,  ,  ,  ,  ,  , or salt thereof, R^{NS} comprises an O^6 protected hypoxanthine (e.g., with $-CH_2CH_2Si(Me)_3$). In some embodiments, R^{NS} is O^6-protected inosine. In some embodiments, R^{NS} is O^6-protected deoxyinosine. In some embodiments, R^{NS} is O^6-protected 2'-F inosine. In some embodiments, R^{NS} is O^6-protected 2'-OR modified inosine whose 2'-OR modification is as described herein (e.g., 2'-OMe, 2'-MOE, etc.). Among other things, the present disclosure encompasses the recognition that such a compound has sufficient solubility for oligonucleotide synthesis and can be utilized in oligonucleotide synthesis while a corresponding compound without O^6 protection may not have sufficient solubility for efficient oligonucleotide synthesis. In some embodiments, a phosphoramidite is (1S,3S,3aS)-1-(((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(6-(2-(trimethylsilyl)ethoxy)-9H-purin-9-yl)tetrahydrofuran-3-yl)oxy)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole. In some embodiments, a phosphoramidite is (1S,3S,3aS)-1-(((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(6-(2-(trimethylsilyl)ethoxy)-9H-purin-9-yl)tetrahydrofuran-3-yl)oxy)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole. In some

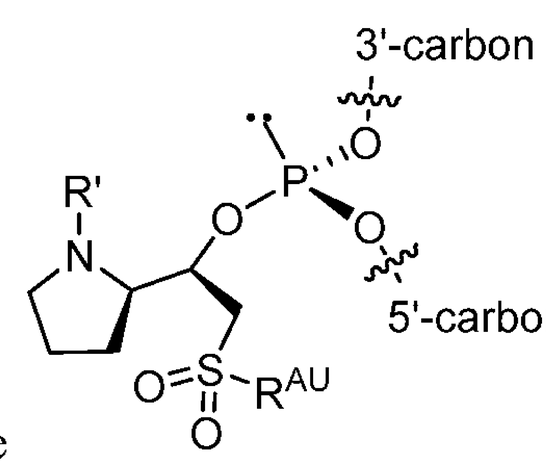
embodiments, in a compound having the structure of  ,  ,  ,  ,  , or  , or salt thereof, R^{NS} comprises an O^6 unprotected hypoxanthine. In some embodiments, R^{NS} is optionally substituted or protected inosine wherein the hypoxanthine is unprotected. In some embodiments, R^{NS} is optionally substituted or protected deoxyinosine wherein the hypoxanthine is unprotected. In some embodiments, R^{NS} is optionally substituted or protected 2'-F inosine wherein the hypoxanthine is unprotected. In some embodiments, R^{NS} is optionally substituted or protected 2'-OR modified inosine wherein the hypoxanthine is unprotected and whose 2'-OR modification is as described herein (e.g., 2'-OMe, 2'-MOE, etc.). Among other things, the present disclosure encompasses the recognition that such a compound has sufficient solubility for oligonucleotide synthesis and can be utilized in oligonucleotide synthesis without O^6 protection.

[00994] In some embodiments, a method comprises providing a DPSE and/or a PSM phosphoramidite or a salt thereof. In some embodiments, a provided method comprises contacting a DPSE and/or a PSM phosphoramidite or a salt thereof with −OH (e.g., 5'−OH of a nucleoside or an oligonucleotide chain). As those skilled in the art appreciate, contacting can be performed under various suitable conditions so that a phosphorus linkage is formed. In some embodiments, preparation of each chirally controlled internucleotidic linkage independently comprises contacting a DPSE or PSM phosphoramidite or a salt thereof with −OH (e.g., 5'−OH of a nucleoside or an oligonucleotide chain). In some embodiments, preparation of each chirally controlled phosphorothioate internucleotidic linkage independently comprises contacting a DPSE phosphoramidite or a salt thereof with −OH (e.g., 5'−OH of a nucleoside or an oligonucleotide chain). In some embodiments, preparation of each chirally controlled non-negatively charged internucleotidic linkage (e.g., n001) independently comprises contacting a PSM phosphoramidite or a salt thereof with −OH (e.g., 5'−OH of a nucleoside or an oligonucleotide chain). In some embodiments, preparation of each chirally controlled internucleotidic linkage independently comprises contacting a PSM phosphoramidite or a salt thereof with −OH (e.g., 5'−OH of a nucleoside or an oligonucleotide chain). In some embodiments, contacting forms a P(III) linkage comprising a phosphorus atom bonded to two sugars and a chiral auxiliary moiety (e.g.,  or  , or a salt form thereof (e.g., from DPSE phosphoramidites or

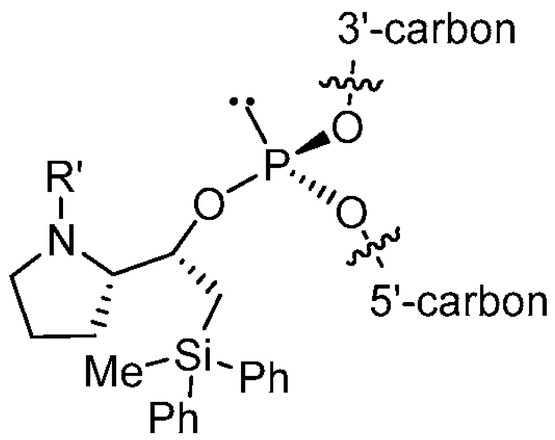
salts thereof),  or  , or a salt form thereof (wherein R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), etc.). In some embodiments, an oligonucleotide comprises a P(III) linkage comprising a chiral auxiliary moiety, e.g., from a DPSE or PSM phosphoramidite. In some embodiments, a P(III) linkage comprising a chiral auxiliary moiety is chirally controlled. In some embodiments, a chiral auxiliary moiety may be protected, e.g., before converting a P(III) linkage to a P(V) linkage (e.g., before sulfurization, reacting with azide, etc.). In some embodiments, a protected chiral auxiliary has the structure of  or  , or a salt form thereof (e.g., wherein R' is independently as described herein; e.g., from DPSE phosphoramidites or salts thereof), or  or  , or a salt form thereof (wherein each R' and R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), wherein each R' is independently as described herein. In some embodiments, R' is −C(O)R, wherein R is as described herein. In some embodiments, R is $-CH_3$. In some embodiments, an oligonucleotide comprises a protected chiral auxiliary. In some embodiments, each chirally controlled internucleotidic linkage in an oligonucleotide independently comprises  or  , or a salt form thereof, or  or  , or a salt form thereof. In some embodiments, each chirally controlled internucleotidic linkage in an oligonucleotide independently comprises  or  , or a salt form thereof. In some embodiments, R' is −C(O)R. In some embodiments, R' is $-C(O)CH_3$. In some embodiments, R^{AU} is Ph. In



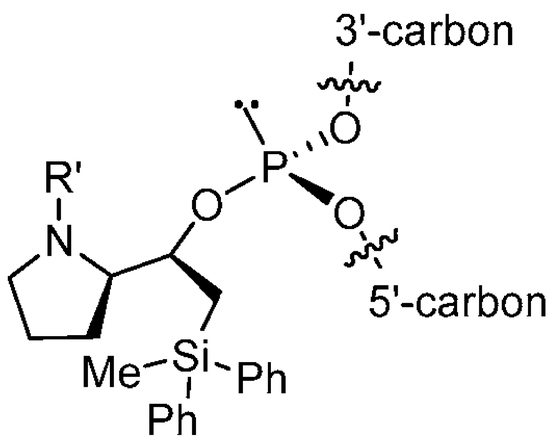
some embodiments, an oligonucleotide comprises one or more or a salt form thereof (PIII-1), wherein each variable independently as described herein. In some embodiments, an

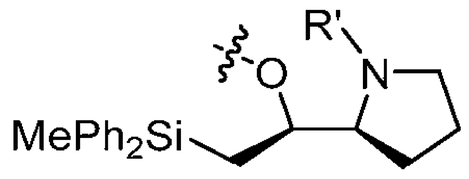


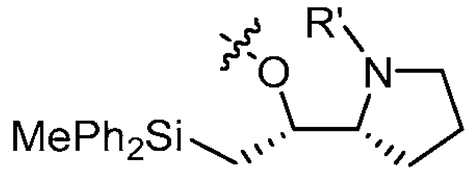
oligonucleotide comprises one or more or a salt form thereof (PIII-2) , wherein each variable independently as described herein. In some embodiments, an oligonucleotide comprises one or



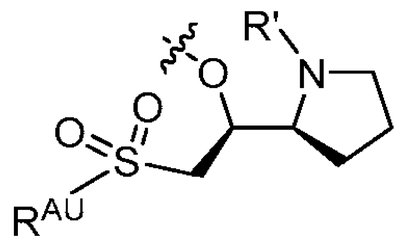
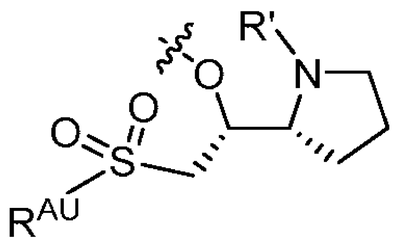
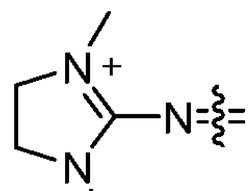
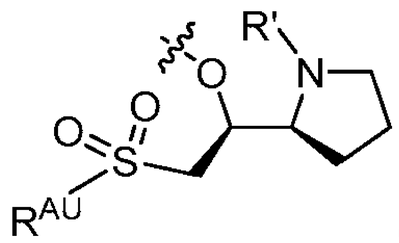
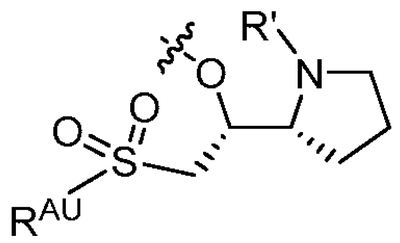
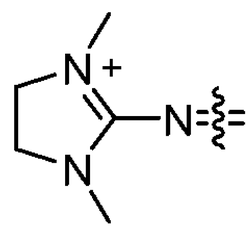
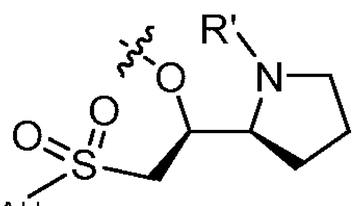
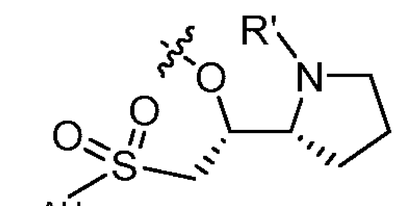
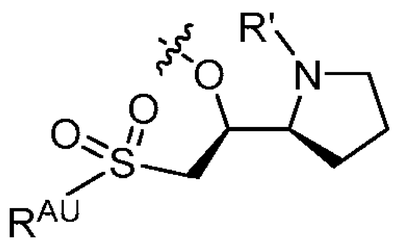
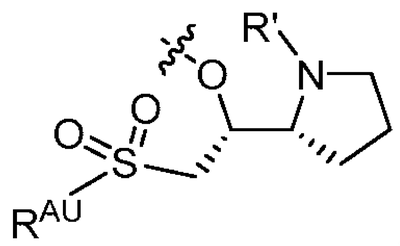
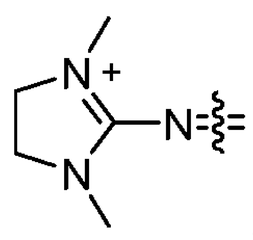
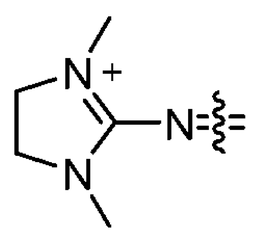
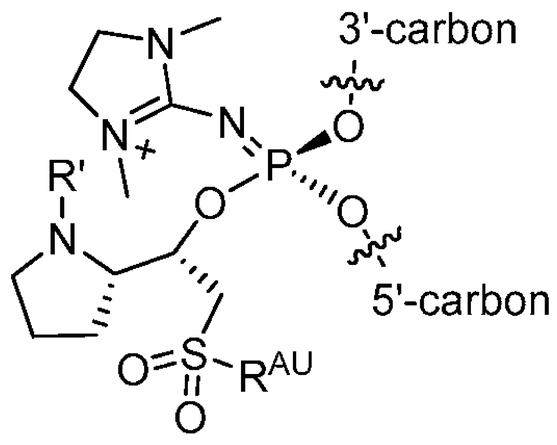
more or a salt form thereof (PIII-5) , wherein each variable independently as described herein. In some embodiments, an oligonucleotide comprises one or more



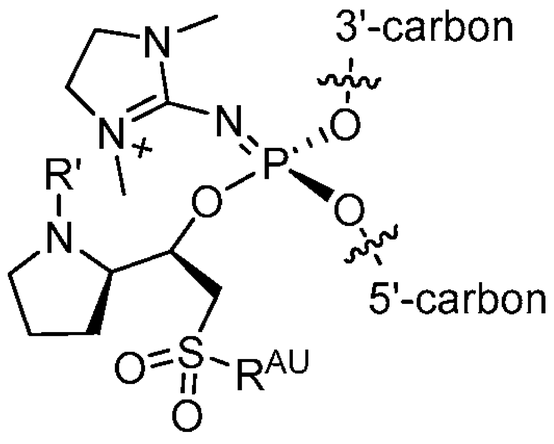
or a salt form thereof (PIII-6) , wherein each variable independently as described herein. In some embodiments, a 5'-end internucleotidic linkage is PIII-1, PIII-2, PIII-5, or PIII-6. In some embodiments, a 5'-end internucleotidic linkage is PIII-1 or PIII-2. In some embodiments, R' is –H. In some embodiments, R' is –C(O)R. In some embodiments, R' is $-C(O)CH_3$. In some embodiments, R^{AU} is –Ph. In some embodiments, a P(III) linkage is converted into a P(V) linkage. In some embodiments, a P(V) linkage comprises a phosphorus atom bonded to two sugars, a chiral auxiliary moiety (e.g., 

or 

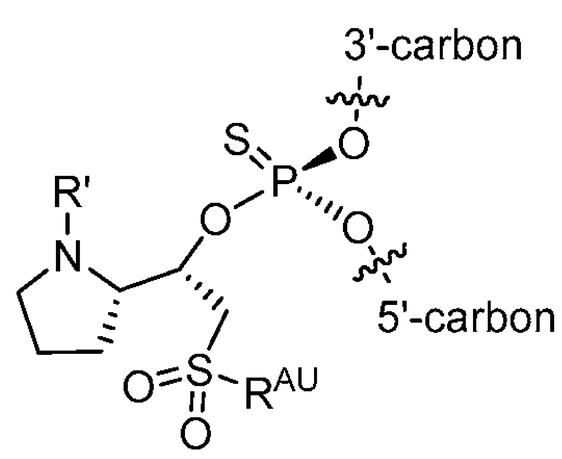
, or a salt form thereof (wherein R' is as described herein; e.g., from DPSE

phosphoramidites or salts thereof),  or  , or a salt form thereof (wherein each of R' and R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), etc.), and S or  . In some embodiments, a P(V) linkage comprises a phosphorus atom bonded to two sugars,  or  , or a salt form thereof (wherein each R' and R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), etc.), and S or  . In some embodiments, a P(V) linkage comprises a phosphorus atom bonded to two sugars,  or  , or a salt form thereof (wherein each R' and R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), etc.), and S. In some embodiments, a P(V) linkage comprises a phosphorus atom bonded to two sugars,  or  , or a salt form thereof (wherein each R' and R^{AU} is independently as described herein; when R^{AU} is −Ph, e.g., from PSM phosphoramidites or salts thereof), etc.), and  . Those skilled in the art will appreciate that  can exist with a counterion, e.g., in some embodiments, PF_6^-. In some embodiments, an oligonucleotide comprises one or more  or a salt form thereof (PV-1) , wherein each variable independently as

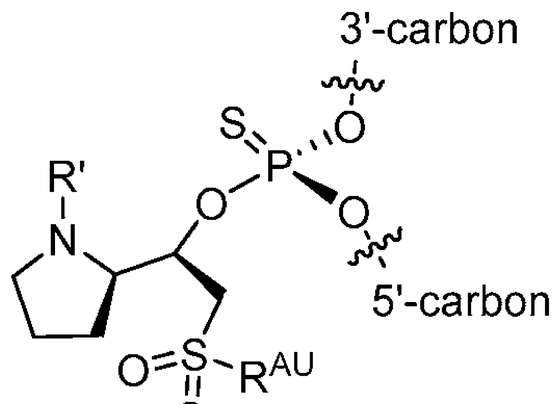
described herein. In some embodiments, an oligonucleotide comprises one or more



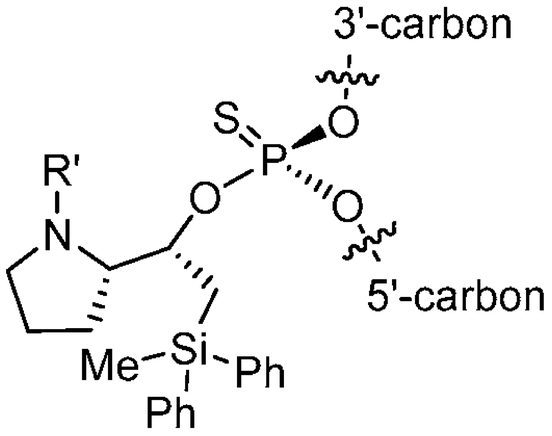
or a salt form thereof (PV-2) , wherein each variable independently as described



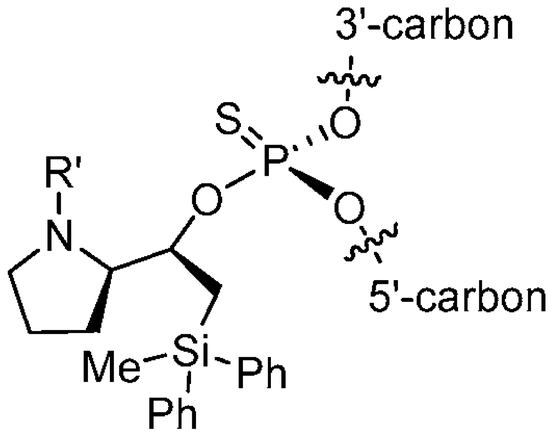
herein. In some embodiments, an oligonucleotide comprises one or more or a salt form thereof (PV-3) , wherein each variable independently as described herein. In some embodiments, an



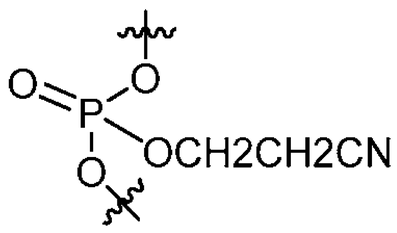
oligonucleotide comprises one or more O or a salt form thereof (PV-4) , wherein each variable independently as described herein. In some embodiments, an oligonucleotide comprises one or



more or a salt form thereof (PV-5) , wherein each variable independently as described herein. In some embodiments, an oligonucleotide comprises one or more



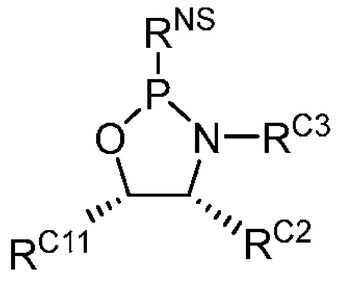
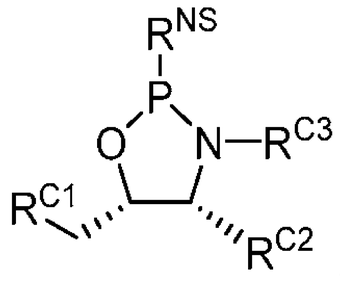
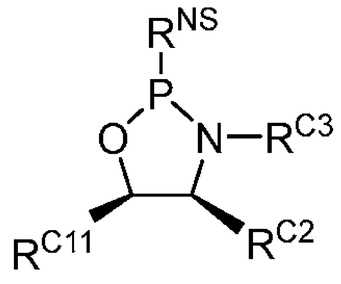
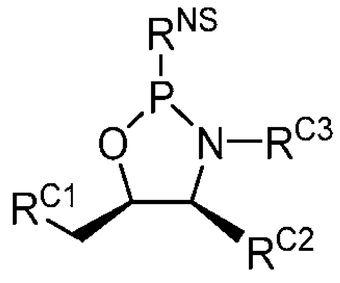
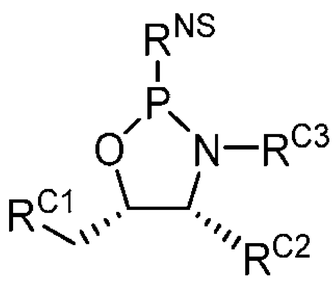
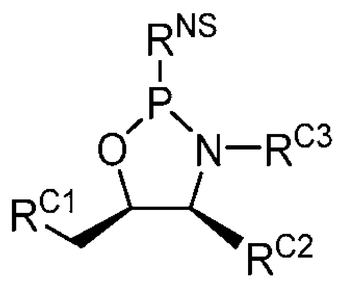
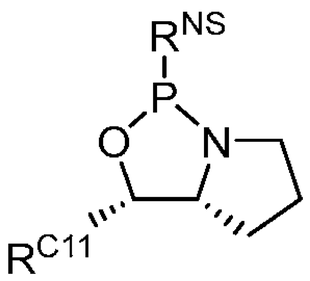
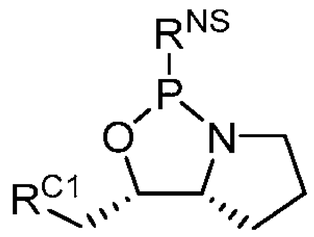
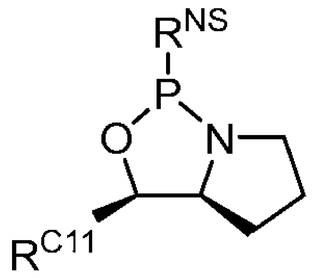
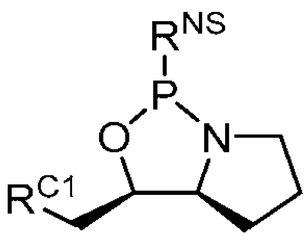
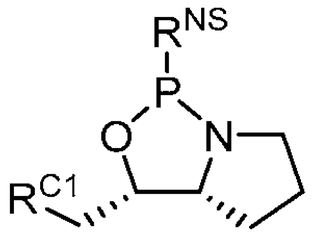
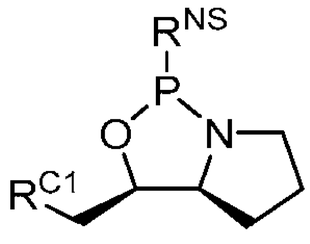
or a salt form thereof (PV-6) , wherein each variable independently as described herein. In some embodiments, each chiral internucleotidic linkage, or each chirally controlled internucleotidic linkage, of an oligonucleotide is independently selected from PIII-1, PIII-2, PIII-5, PIII-6, PV-1, PV-2, PV-3,

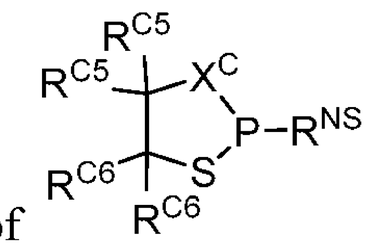
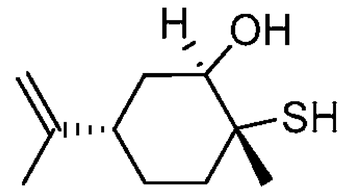
PV-4, PV-5, and PV-6. In some embodiments, each chiral internucleotidic linkage, or each chirally controlled internucleotidic linkage, of an oligonucleotide is independently selected from PIII-1, PIII-2, PV-1, PV-2, PV-3, and PV-4. In some embodiments, a linkage of PIII-1, PIII-2, PIII-5, or PIII-6 is typically the 5'-end internucleotidic linkage. In some embodiments, each chiral internucleotidic linkage, or each chirally controlled internucleotidic linkage, of an oligonucleotide is independently selected from PV-1, PV-2, PV-3, PV-4, PV-5, and PV-6. In some embodiments, each chiral internucleotidic linkage, or each chirally controlled internucleotidic linkage, of an oligonucleotide is independently selected from PV-1, PV-2, PV-3, or PV-4. In some embodiments, a provided oligonucleotide is an oligonucleotide as described herein, e.g., of Table 1, wherein each *S is independently replaced with PV-3 or PV-5, each *R is independently replaced with PV-4 or PV-6, each n001R is independently replaced with PV-1, and each n001S is independently replaced with PV-2. In some embodiments, a provided oligonucleotide is an oligonucleotide as described herein, e.g., of Table 1, wherein each *S is independently replaced with PV-3, each *R is independently replaced with PV-4, each n001R is independently replaced with PV-1, and each n001S is independently replaced with PV-2. In some embodiments, each natural phosphate linkage is independently replaced with a precursor, e.g., 

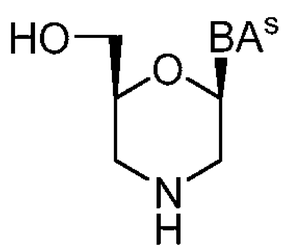
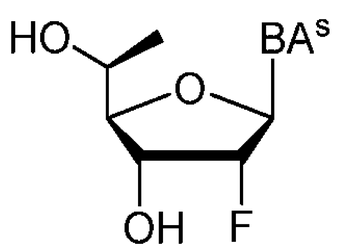
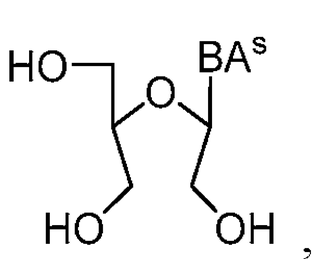
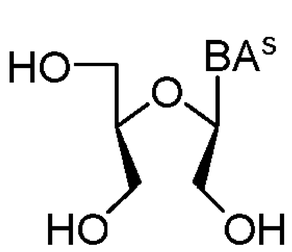
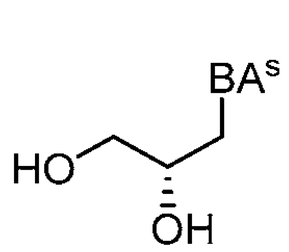
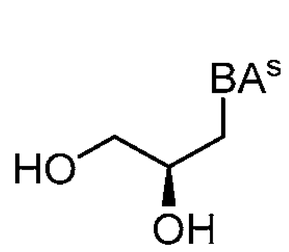
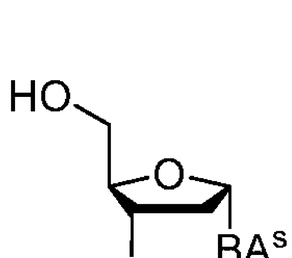
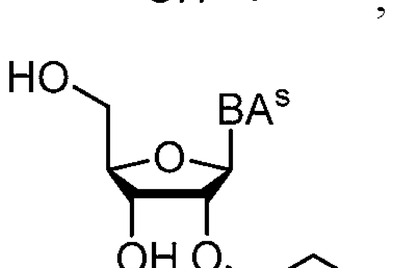
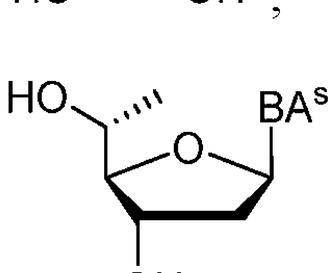
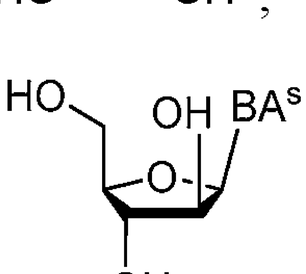
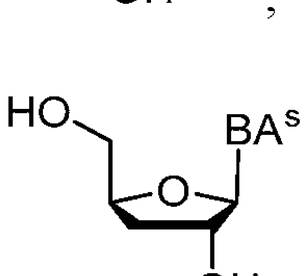
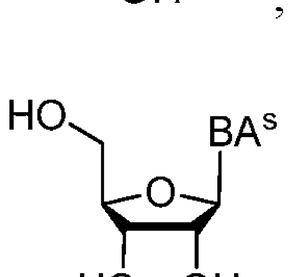
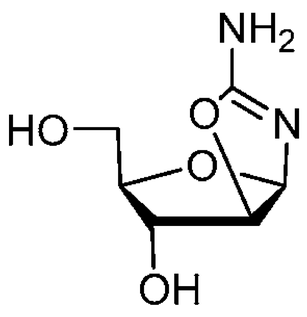
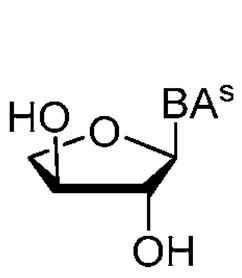
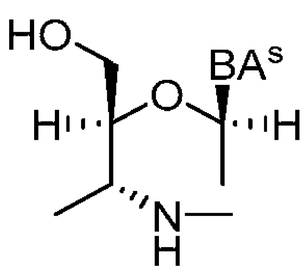
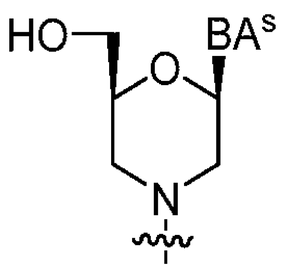
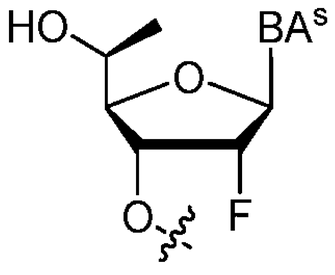
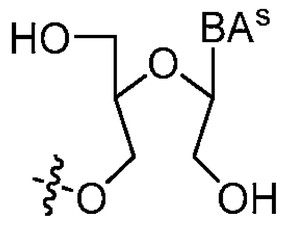
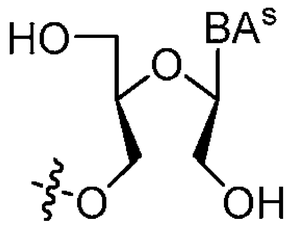
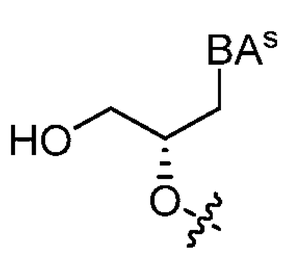
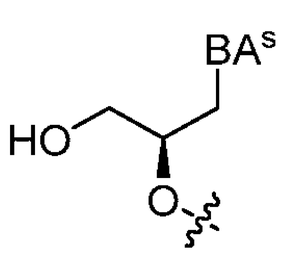
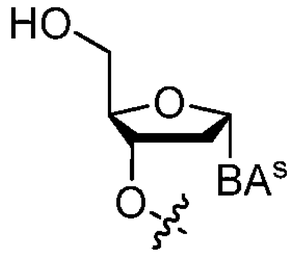
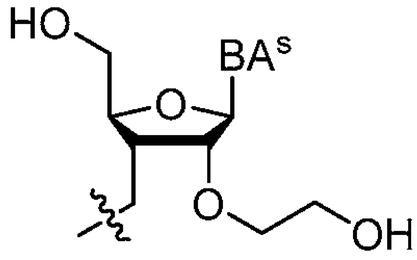
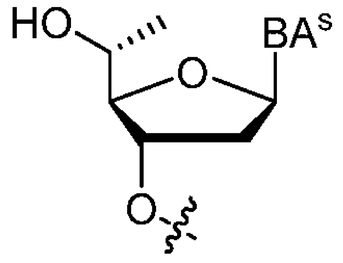
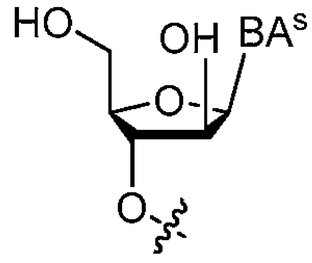
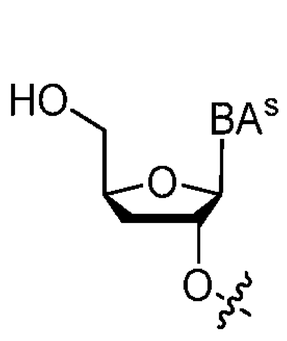
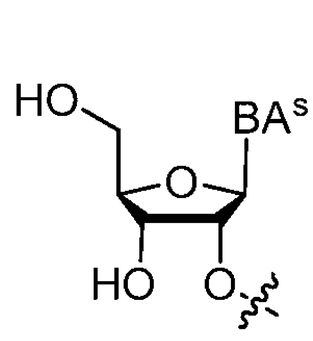
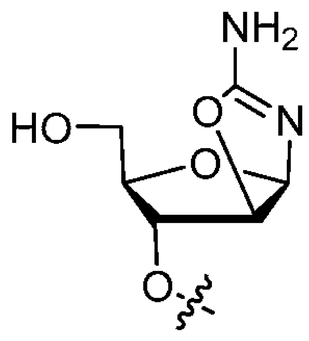
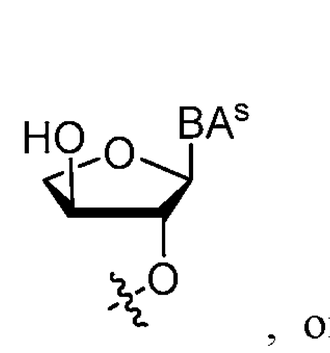
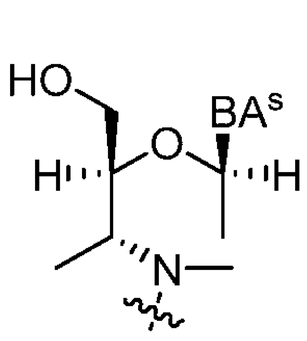
. In some embodiments, R' is −H. In some embodiments, R' is −C(O)R. In some embodiments, R' is $-C(O)CH_3$. In some embodiments, R^{AU} is −Ph. In some embodiments, a method comprises removal of one or more chiral auxiliary moieties so that phosphorothioate and/or non-negatively charged internucleotidic linkages (e.g., n001) are formed (e.g., from V-1, PV-2, PV-3, PV-4, PV-5, PV-6, etc.). In some embodiments, removal of a chiral auxiliary (e.g., PSM) comprises contacting an oligonucleotide with a base (e.g., $N(R)_3$ such as DEA) under anhydrous conditions.

[00995] In some embodiments, as appreciated by those skilled in the art, for preparation of a chirally controlled internucleotidic linkage, a monomer or a phosphoramidite (e.g., a DPSE or PSM phosphoramidite) is typically utilized in a chirally enriched or pure form (e.g., of a purity as described herein (e.g., about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, or about 100%)).

[00996] In some embodiments, the present disclosure provides useful reagents for preparation of oligonucleotides and compositions thereof. In some embodiments, monomers and phosphoramidites comprise nucleosides, nucleobases and sugars as described herein. In some embodiments, nucleobases and sugars are properly protected for oligonucleotide synthesis as those skilled in the art will appreciate. In some embodiments, a phosphoramidite has the structure of R^{NS}–P(OR)N$(R)_2$, wherein R^{NS} is a optionally protected nucleoside moiety. In some embodiments, a phosphoramidite has the structure of R^{NS}–P(OCH_2CH_2CN)N(i-Pr)$_2$. In some embodiments, a monomer comprises a nucleobase which is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is

optionally substituted or protected. In some embodiments, a phosphoramidite comprises a nucleobase which is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected. In some embodiments, a phosphoramidite comprises a chiral auxiliary moiety, wherein the phosphorus is bonded to an oxygen and a nitrogen atom of the chiral auxiliary moiety. In some embodiments, a phosphoramidite has the structure of  ,  ,  , or  , or a salt thereof, wherein R^{NS} is a protected nucleoside moiety (e.g., 5'-OH and/or nucleobases suitably protected for oligonucleotide synthesis), and each other variable is independently as described herein. In some embodiments, a phosphoramidite has the structure of  or  , wherein R^{NS} is a protected nucleoside moiety (e.g., 5'-OH and/or nucleobases suitably protected for oligonucleotide synthesis), R^{C1} is R, $-Si(R)_3$ or $-SO_2R$, and R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms, wherein the coupling forms an internucleotidic linkage. In some embodiments, 5'-OH of R^{NS} is protected. In some embodiments, 5'-OH of R^{NS} is protected as $-$ODMTr. In some embodiments, R^{NS} is bonded to phosphorus through its 3'-O-. In some embodiments, a formed ring by R^{C2} and R^{C3} is an optionally substituted 5-membered ring. In some embodiments, a phosphoramidite has the structure of  ,  ,  or  , or a salt thereof. In some embodiments, a phosphoramidite has the structure of  or  . In some embodiments, as described herein R^{NS} comprises a modified nucleobase (e.g., b001A, b002A, b003A, b008U, b001C, etc.) which is optionally protected for

oligonucleotide synthesis. In some embodiments, a monomer has the structure of  or a salt thereof, wherein R^{NS} is an optionally substituted/protected nucleoside (e.g., optionally protected for oligonucleotide synthesis) as described herein, and each other variable is independently as described herein. In some embodiments, $-X^C-C(R^{C5})_2-C(R^{C6})_2-S-$ is of such a structure that $H-X^C-C(R^{C5})_2-C(R^{C6})_2-SH$ is a compound as described herein, e.g., $HOCH(CH_3)CH(CH_3)SH$, $HSCH(CH_3)CH(CH_3)SH$,  , etc. In some embodiments, 5'-OH of R^{NS} is protected. In some embodiments, 5'-OH of R^{NS} is protected as $-ODMTr$.

[00997] In some embodiments, R^{NS} is an optionally substituted or protected nucleoside selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , or a salt thereof, wherein BA^s is as described herein. In some embodiments, R^{NS} is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or , or a salt thereof,

wherein BA^s is as described herein. In some embodiments, each −OH is optionally and independently substituted or protected. In some embodiments, BA^s is optionally substituted or protected nucleobase, and each −OH of the nucleoside is independently protected, wherein at least one −OH is protected as DMTrO−. In some embodiments, −OH for coupling, e.g., with another monomer or phosphoramidite, is protected as DMTrO−. In some embodiments, an −OH group for coupling, e.g., with another monomer or phosphoramidite, is protected different from an −OH group that is not for coupling. In some embodiments, a non-coupling −OH is protected such that the protection remains when DMTrO− is deprotected. In some embodiments, a non-coupling −OH is protected such that the protection remains during oligonucleotide synthesis cycles. In some embodiments, BA^s is an optionally protected nucleobase selected from A, T, C, G, U, and tautomers thereof.

[00998] In some embodiments, purity or stereochemical purity of a monomer or a phosphoramidite is at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, it is at least 85%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%.

[00999] In some embodiments, the present disclosure provides a method for preparing an oligonucleotide or composition, comprising coupling a free −OH, e.g., a free 5'-OH, of an oligonucleotide or a nucleoside with a monomer as described herein. In some embodiments, the present disclosure provides a method for preparing an oligonucleotide or composition, comprising coupling a free −OH, e.g., a free 5'-OH, of an oligonucleotide or a nucleoside with a phosphoramidite as described herein.

[001000] In some embodiments, the present disclosure provides an oligonucleotide, wherein the oligonucleotide comprises one or more modified internucleotidic linkages each independently having the structure of $-O^5-P^L(W)(R^{CA})-O^3-$, wherein:

P^L is P, or P(=W);

W is O, S, or W^N;

W^N is $=N-C(-N(R^1)_2=N^+(R^1)_2Q^-$;

Q^- is an anion;

R^{CA} is or comprises an optionally capped chiral auxiliary moiety,

O^5 is an oxygen bonded to a 5'-carbon of a sugar, and

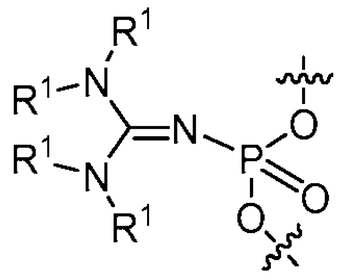
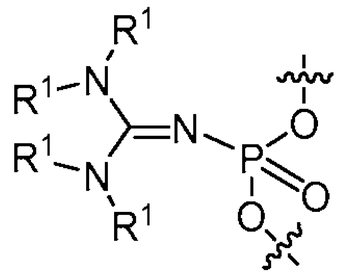
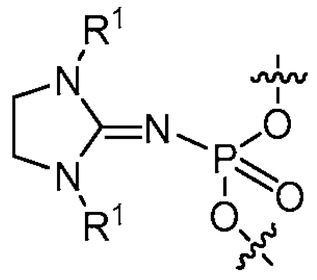
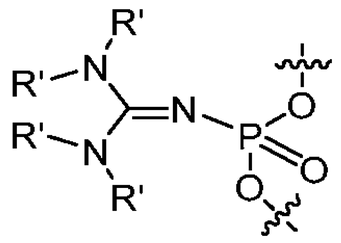
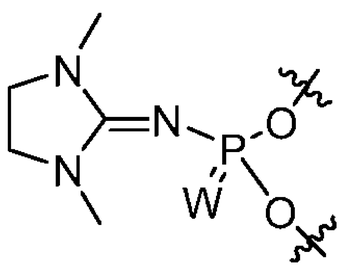
O^3 is an oxygen bonded to a 3'-carbon of a sugar.

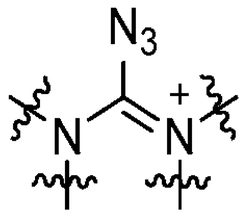
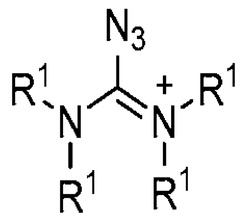
[001001] In some embodiments, a modified internucleotidic linkage is optionally chirally controlled. In some embodiments, a modified internucleotidic linkage is optionally chirally controlled.

[001002] In some embodiments, a provided methods comprising removing R^{CA} from such a modified internucleotidic linkages. In some embodiments, after removal, bonding to R^{CA} is replaced with −OH. In some embodiments, after removal, bonding to R^{CA} is replaced with =O, and bonding to W^N is replaced with $-N=C(N(R^1)_2)_2$.

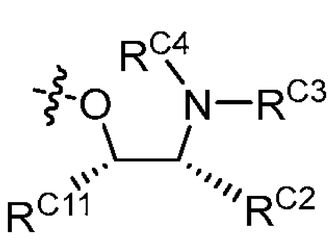
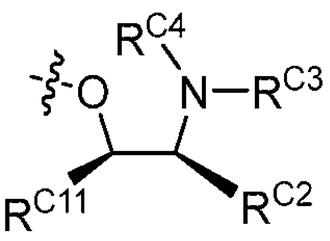
[001003] In some embodiments, P^L is P=S, and when R^{CA} is removed, such an internucleotidic linkage is converted into a phosphorothioate internucleotidic linkage.

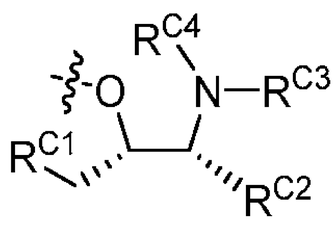
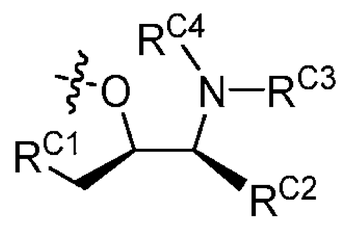
[001004] In some embodiments, P^L is $P=W^N$, and when R^{CA} is removed, such an internucleotidic linkage is

converted into an internucleotidic linkage having the structure of  . In some embodiments, an internucleotidic linkage having the structure of  has the structure of  . In some embodiments, an internucleotidic linkage having the structure of  has the structure of  .

[001005] In some embodiments, P^L is P (e.g., in newly formed internucleotidic linkage from coupling of a phosphoramidite with a 5'-OH). In some embodiments, W is O or S. In some embodiments, W is S (e.g., after sulfurization). In some embodiments, W is O (e.g., after oxidation). In some embodiments, certain non-negatively charged internucleotidic linkages or neutral internucleotidic linkages may be prepared by reacting a P(III) phosphite triester internucleotidic linkage with azido imidazolinium salts (*e.g.*, compounds comprising ) under suitable conditions. In some embodiments, an azido imidazolinium salt is a salt of PF_6^-. In some embodiments, an azido imidazolinium salt is a slat of  . In some embodiments, an azido imidazolinium salt is 2-azido-1,3-dimethylimidazolinium hexafluorophosphate.

[001006] As appreciated by those skilled in the art, Q^- can be various suitable anion present in a system (e.g., in oligonucleotide synthesis), and may vary during oligonucleotide preparation processes depending on cycles, process stages, reagents, solvents, etc. In some embodiments, Q^- is PF_6^-.

[001007] In some embodiments, R^{CA} is  or  , wherein R^{C4} is –H or –C(O)R', and each other variable is independently as described herein. In some embodiments, R^{CA} is

or , wherein R^{C1} is R, −Si(R)$_3$ or −SO$_2$R, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms, R^{C4} is −H or −C(O)R'. In some embodiments, R^{C4} is −H. In some embodiments, R^{C4} is −C(O)CH$_3$. In some embodiments, R^{C2} and R^{C3} are taken together to form an optionally substituted 5-membered ring.

[001008] In some embodiments, R^{C4} is −H (e.g., in n newly formed internucleotidic linkage from coupling of a phosphoramidite with a 5'-OH). In some embodiments, R^{C4} is −C(O)R (e.g., after capping of the amine). In some embodiments, R is methyl.

[001009] In some embodiments, each chirally controlled phosphorothioate internucleotidic linkage is independently converted from $-O^5-P^L(W)(R^{CA})-O^3-$.

Assessment/Characterization of Providing Technologies

[001010] As appreciated by those skilled in the art, various technologies may be utilized to assess/characterize provided technologies in accordance with the present disclosure. Certain useful technologies are described in the Examples; as demonstrated, among other things, the present disclosure describes various *in vivo* and *in vitro* technologies suitable for assessing and characterizing provided technologies. In some embodiments, provided technologies are assessed/characterized, e.g., in cells, with or without exogenous ADAR polypeptides; additionally or alternatively, in some embodiments, provided technologies are assessed/characterized, e.g., in animals, e.g., non-human primates and mice.

[001011] Among other things, the present disclosure encompasses the insights that various agents (e.g., oligonucleotides) and compositions thereof that can provide editing in various human systems, e.g., cells, may show no or much lower levels of editing in certain cells (e.g., mouse cells) and certain animals such as rodents (e.g., mice) that do not contain or express human ADAR, e.g., human ADAR1. Particularly, mice, a commonly used animal model, may be of limited uses for assessing various agents (e.g., oligonucleotides) for editing in humans, as various agents active in human cells provide no or very low levels of activity in mouse cells and animals not engineered to comprise or express a proper ADAR1 (e.g., human ADAR1) polypeptide or a characteristic portion thereof. In some embodiments, the present disclosure provides engineered cells and non-human animals expressing human ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, such cells and human are useful for assessing and characterizing provided technologies. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1 p110 polypeptide or a characteristic portion thereof. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises

human ADAR1 p150 polypeptide or a characteristic portion thereof. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises a human ADAR1 p110 peptide. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises a human ADAR1 p150 peptide. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises one or more or all of the following domains of human ADAR1: Z-DNA binding domains, dsRNA binding domains, and deaminase domain. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises one or both of human ADAR1 Z-DNA binding domains; alternatively or additionally, in some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises one, two or all of human ADAR1 dsRNA binding domains; alternatively or additionally, a human ADAR1 polypeptide or a characteristic portion thereof is or comprises a human deaminase domain. In some embodiments, a human ADAR1 polypeptide or a characteristic portion thereof may be expressed together with a mouse ADAR1 polypeptide or a characteristic portion thereof, e.g., one or more human dsRNA binding domains may be engineered to be expressed together with a mouse deaminase domain to form a human-mouse hybrid ADAR1 polypeptide. In some embodiments, cells and/or non-human animals are engineered to comprise and/or express a polynucleotide encoding a human ADAR1 polypeptide or a characteristic portion thereof as described herein. In some embodiments, genomes of cells and/or non-human animals are engineered to comprise a polynucleotide encoding a human ADAR1 polypeptide or a characteristic portion thereof as described herein. In some embodiments, germline genomes of cells and/or non-human animals are engineered to comprise a polynucleotide encoding a human ADAR1 polypeptide or a characteristic portion thereof as described herein. In some embodiments, cells and non-human animals are engineered to comprise, e.g., in their genomes (in some embodiments, germline genomes), one or more G to A mutations each independently associated with a condition, disorder or disease (e.g., a mutation (e.g., c. 1024G>A) in SERPINA1 gene that leads to a glutamate to lysine substitution at amino acid position 342 (E342K) of an A1AT protein). As demonstrated herein, among other things such cells and animals are useful for assessing/characterizing provided technologies, e.g., various oligonucleotides and compositions thereof, e.g., for their editing properties and/or activities, including for their uses against one or more conditions, disorders or diseases. In some embodiments, cells are rodent cells. In some embodiments, cells are mouse cells. In some embodiments, an animal is a rodent. In some embodiments, an animal is a mice.

[001012] Among other things, the present disclosure provides oligonucleotide designs comprising sugar modifications, base modifications, internucleotidic linkage modifications, linkage phosphorus stereochemistry, and/or patterns thereof, that can greatly improve one or more properties and/or activities of oligonucleotides compared to comparable oligonucleotides of similar or identical base sequences but of reference designs. For example, it was observed that oligonucleotides of various provided designs and compositions thereof can provide high levels of editing in mice that do not express a human ADAR protein (e.g., mice only expressing mouse ADAR proteins), in some embodiments comparable to or no lower than in

mice that are engineered to express a human ADAR protein, while comparable oligonucleotides of reference designs and compositions thereof provide low levels of editing in mice that do not express a human ADAR protein (e.g., mice only expressing mouse ADAR proteins), in some embodiments significantly lower than in mice that are engineered to express a human ADAR protein. In some embodiments, a reference design is a design reported in WO 2016/097212, WO 2017/220751, WO 2018/041973, WO 2018/134301A1, WO 2019/158475, WO 2019/219581, WO 2020/157008, WO 2020/165077, WO 2020/201406 or WO 2020/252376. In some embodiments, a reference design is a design in WO 2021/071858.

[001013] In some embodiments, the present disclosure provides technologies for assessing/characterizing for assessing cells and/or non-human animals, including those engineered to comprise or express an ADAR1 polypeptide or a characteristic portion thereof, or a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof, which ADAR1 polypeptide or a characteristic portion thereof and/or polynucleotide is not in and/or is not expressed in the cells and/or non-human animals prior to engineering. In some embodiments, a provided method comprises administering to a cell or a population thereof one or more oligonucleotides or compositions which one or more oligonucleotides or compositions can each independently edit an adenosine in a comparable human cell or a population thereof. In some embodiments, a provided method comprises administering to an animal or a population thereof one or more oligonucleotides or compositions which one or more oligonucleotides or compositions can each independently edit an adenosine in a human cell or a population thereof. In some embodiments, editing levels in cells to be assessed/characterized, or in cells from animals, are compared to those observed in comparable human cells. In some embodiments, comparable human cells are of the same type as cells to be assessed/characterized or cells from animals. In some embodiments, cells are rodent cells. In some embodiments, cells are mouse cells. In some embodiments, an animal is a rodent. In some embodiments, an animal is a mice. In some embodiments, one or more oligonucleotides or compositions are administered separately to separate cells and/or animals. In some embodiments, one or more oligonucleotides or compositions may be administered to the same collection of cells and/or animals, optionally simultaneously. Various oligonucleotides and compositions that can edit various target adenosines are as described herein and can be utilized accordingly.

[001014] As appreciated by those skilled in the art, in some embodiments, provided technologies, e.g., oligonucleotides, compositions, etc., may be assessed in one or more models, e.g., cells, tissues, organs, animals, etc. In some embodiments, as appreciated by those skilled in the art, cells, tissues, organs, animals, etc. are or comprise cells of, associated with or comprising one or more characteristics (e.g., nucleotide sequences such as mutations) of conditions, disorders or diseases. For example, in some embodiments, cells, tissues, organs, animals, etc. comprise G to A mutations associated with conditions, disorders or diseases, e.g., 1024G>A (E342K) in human SERPINA1. In some embodiments, an animal is a NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ mouse (e.g., see The Jackson Laboratory Stock No: 028842; NSG-PiZ, and also Borel F; Tang Q; Gernoux G; Greer C; Wang Z; Barzel A; Kay MA; Shultz LD; Greiner DL; Flotte TR; Brehm MA; Mueller C. 2017. Survival Advantage of Both Human Hepatocyte Xenografts and

Genome-Edited Hepatocytes for Treatment of alpha-1 Antitrypsin Deficiency. Mol Ther 25(11):2477-2489PubMed: 29032169MGI: J:243726, and Li S; Ling C; Zhong L; Li M; Su Q; He R; Tang Q; Greiner DL; Shultz LD; Brehm MA; Flotte TR; Mueller C; Srivastava A; Gao G. 2015). Efficient and Targeted Transduction of Nonhuman Primate Liver With Systemically Delivered Optimized AAV3B Vectors. Mol Ther 23(12):1867-76PubMed: 26403887MGI: J:230567). In some embodiments, cells, tissues, organs, animals, etc. comprise one or more cancer cells. In some embodiments, non-human cells, tissues, organs, animals, etc. are engineered to comprise or express ADAR1 or a characteristic portion thereof, e.g., through incorporation of (optionally into its genome or germline genome) a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, an ADAR1 is a primate ADAR1. In some embodiments, an ADAR1 is a human ADAR1. In some embodiments, a human ADAR1 is human ADAR1 p110. In some embodiments, a human ADAR1 is human ADAR1 p150. As appreciated by those skilled in the art, various technologies are available in the art and can be utilized in accordance with the present disclosure to generated useful cells, tissues, organs, animals, etc. For example, for condition, disorder or disease animal models expressing human ADAR1 or a characteristic portion thereof, an animal model can be crossed with huADAR1 mice described herein to provide engineered animal models expressing human ADAR1 or a characteristic portion thereof. In some embodiments, mice comprising G to A mutations, e.g., a NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ mouse (e.g., see The Jackson Laboratory Stock No: 028842; NSG-PiZ, and also Borel F; Tang Q; Gernoux G; Greer C; Wang Z; Barzel A; Kay MA; Shultz LD; Greiner DL; Flotte TR; Brehm MA; Mueller C. 2017. Survival Advantage of Both Human Hepatocyte Xenografts and Genome-Edited Hepatocytes for Treatment of alpha-1 Antitrypsin Deficiency. Mol Ther 25(11):2477-2489PubMed: 29032169MGI: J:243726, and Li S; Ling C; Zhong L; Li M; Su Q; He R; Tang Q; Greiner DL; Shultz LD; Brehm MA; Flotte TR; Mueller C; Srivastava A; Gao G. 2015) are crossed with huADAR1 mice described herein to provide mice comprising G to A mutations (e.g., 024G>A (E342K) in human SERPINA1) and expressing human ADAR1 or a characteristic portion thereof.

[001015] As appreciated by those skilled in the art, in some embodiments, animals can be heterozygous with respect to one or more or all sequences. In some embodiments, animals are homozygous with respect to one or more or all sequences. In some embodiments, animals are hemizygous with respect to one or more or all engineered sequences. In some embodiments, animals are homozygous with respect to one or more sequences, and heterozygous with respect to one or more sequences. In some embodiments, animals are heterozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, animals are homozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, certain animals are heterozygous with respect to one or more polynucleotide sequences associated with various condition, disorder or diseases, and are heterozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, certain animals are homozygous with respect to one or more polynucleotide sequences associated with various condition, disorder or diseases, and

are heterozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, certain animals are heterozygous with respect to one or more polynucleotide sequences associated with various condition, disorder or diseases, and are homozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, certain animals are homozygous with respect to one or more polynucleotide sequences associated with various condition, disorder or diseases, and are homozygous with respect to a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. Cells or tissues may be similarly heterozygous, hemizygous and/or homozygous with respect to various sequences.

[001016] In some embodiments, the present disclosure provides methods for assessing an agent, e.g., an oligonucleotide, or a composition thereof, comprising administering to an animal, cell or tissue described herein the agent or composition. In some embodiments, an agent or composition is assessed for preventing or treating a condition, disorder or disease. In some embodiments, animals, cells, tissues, e.g., as described in various embodiments herein, are animal models, or cells or tissues, for various conditions, disorders or diseases (e.g., comprising mutations associated with various conditions, disorders or diseases, and/or cells, tissues, organs, etc., associated with or of various conditions, disorders or diseases) that are engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, animals may be provided by breeding (e.g., IVF, natural breeding, etc.) an animal that are model animals for various conditions, disorders or diseases but are not engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof with animals that are engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, cells or tissues may be provided by introducing into cells or tissues a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease, comprising administering to a subject an effective amount of an agent or a compositions thereof, wherein the agent or composition is assessed in an animal provided herein (e.g., an animal engineered to comprise an ADAR1 polypeptide or a characteristic portion thereof, an animal engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof, a model animal for a condition, disorder or disease which is engineered to comprise an ADAR1 polypeptide or a characteristic portion thereof, a model animal for a condition, disorder or disease engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof). In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease, comprising administering to a subject an effective amount of an agent or a compositions thereof, wherein the agent or composition is assessed in a cell or tissue provided herein. In some embodiments, an animal, cell or tissue comprises a SERPINA1 mutation (e.g., 1024 G>A (E342K)) and is engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some

embodiments, an animal is a non-human animal. In some embodiments, cells are non-human animal cells. In some embodiments, tissues are non-human animal tissues. In some embodiments, a non-human animal is a rodent. In some embodiments, a non-human animal is a mouse. In some embodiments, a non-human animal is a rat. In some embodiments, a non-human animal is a non-human primate.

[001017] In some embodiments, the present disclosure provides methods comprising: 1) assessing an agent or a composition thereof, comprising contacting the agent or a composition thereof with a provided cell or tissue associated with or of a condition, disorder or disease, and 2) administering to a subject suffering from or susceptible to a condition, disorder or disease an effective amount of an agent or composition thereof. In some embodiments, the present disclosure provides methods comprising: 1) assessing an agent or a composition thereof, comprising administering the agent or a composition thereof to a provided animal which is an animal model of a condition, disorder or disease, and 2) administering to a subject suffering from or susceptible to a condition, disorder or disease an effective amount of an agent or composition thereof. In some embodiments, as described herein, a cell, tissue or animal is engineered to comprise an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, a cell, tissue or animal is engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, a cell, tissue or animal further comprises a nucleotide sequence (e.g., a mutation) associated with a condition, disorder or disease. In some embodiments, an animal is a rodent, e.g., a mouse, a rat, etc. In some embodiments, a cell or tissue is of a rodent, e.g., a mouse, a rat, etc. In some embodiments, a cell is a germline cell. In some embodiments, a fraction of and not all cells, e.g., cells of particular cell types or tissues or location, of a population of cells, a tissue or an animal comprise a nucleotide sequence (e.g., a mutation) associated with a condition, disorder or disease, and such fraction of cells are engineered to comprise an ADAR1 polypeptide or a characteristic portion thereof or engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, a collection of liver cells comprise a SERPINA1 mutation, e.g., 1024 G>A (E342K) and a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. Those skilled in the art appreciate that various technologies are available for optionally controlled introduction and/or expression of a nucleotide sequence in various cells, tissues, or organs and can be utilized in accordance with the present disclosure. In some embodiments, as described herein, a cell, tissue or animal comprises a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof in a genome, in some embodiments, in a germline genome. In some embodiments, as described herein, a cell, tissue or animal comprises a nucleotide sequence (e.g., a mutation) associated with a condition, disorder or disease in a genome, in some embodiments, in a germline genome.

[001018] As described herein, in some embodiments, a polynucleotide encodes human ADAR1 p110 or a characteristic portion thereof. In some embodiments, a polynucleotide encodes human ADAR1 p110. In some embodiments, a polynucleotide encodes human ADAR1 p150 or a characteristic portion thereof. In some embodiments, a polynucleotide encodes human ADAR1 p150. In some embodiments, a cell, tissue or animal

(e.g., a huADAR mouse or a cell or tissue therefrom) is engineered to comprise and/or express a polynucleotide whose sequence encodes a human ADAR1 p110 polypeptide or a characteristic portion thereof. In some embodiments, a cell, tissue or animal (e.g., a huADAR mouse or a cell or tissue therefrom) is engineered to comprise and/or express a polynucleotide whose sequence encodes a human ADAR1 p110 polypeptide. In some embodiments, a cell, tissue or animal (e.g., a huADAR mouse or a cell or tissue therefrom) is engineered to comprise and/or express a polynucleotide whose sequence encodes a human ADAR1 p150 polypeptide or a characteristic portion thereof. In some embodiments, a cell, tissue or animal (e.g., a huADAR mouse or a cell or tissue therefrom) is engineered to comprise and/or express a polynucleotide whose sequence encodes a human ADAR1 p150 polypeptide. As described herein, in some embodiments, an animal is a rodent, e.g., a mouse or a rat.

[001019] In some embodiments, ADAR (e.g., human ADAR1) transgene is established on a zygote, e.g., SERPINA1 mouse zygote comprising a mutation (e.g., 1024 G>A (E342K) in human SERPINA1) or vice versa. In some embodiments, a zygote is homozygous. In some embodiments, a zygote is heterozygous.

Uses and Applications

[001020] As appreciated by those skilled in the art, oligonucleotides are useful for multiple purposes. In some embodiments, provided technologies (e.g., oligonucleotides, compositions, methods, etc.) can be useful for modulating levels and/or activities of various nucleic acids (e.g., RNA) and/or products encoded thereby (e.g., proteins). In some embodiments, provided technologies can reduce levels and/or activities of undesired target nucleic acids (e.g., comprising undesired adenosine) and/or products thereof. In some embodiments, provided technologies can increase levels and/or activities of desired target nucleic acids (e.g., comprising I instead of undesired adenosine at one or more locations) and/or products thereof.

[001021] For example, in some embodiments, provided technologies can be utilized as single-stranded oligonucleotides for site-directed editing of target adenosine in target RNA sequences. In some embodiments, provided technologies are capable of modulating levels of expressions and activities. Among other things, the present disclosure provides improvement by provided technologies which can be improvement of various desired biological functions, including but not limited to treatment and/or prevention of various conditions, disorders or diseases (e.g., those associated with G to A mutation).

[001022] In some embodiments, provided technologies can modulate activities and/or functions of a target gene. In some embodiments, a target gene is a gene with respect to which expression and/or activity of one or more gene products (e.g., RNA and/or protein products) are intended to be altered. In many embodiments, target genes have target adenosine residues to be altered and can benefit from conversion of such residues to inosine residues. In some embodiments, when an oligonucleotide as described herein acts on a particular target gene, level and/or activity of one or more gene products of that gene can be altered when the oligonucleotide is present as compared with when it is absent.

[001023] In some embodiments, provided oligonucleotides and compositions are useful for treating various

conditions, disorders, or diseases, by reducing levels and/or activities of target transcripts and/or products encoded thereby that are associated with the conditions, disorders, or diseases, and optionally providing transcripts and/or products encoded thereby that are less associated or not associated with the conditions, disorders or diseases (e.g., by conversion of target adenosine to inosine to correct G to A mutations, to alter splicing, etc.). In some embodiments, the present disclosure provides methods for preventing or treating a condition, disorder, or disease, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of a provided oligonucleotide or composition. In some embodiments, the present disclosure provides methods for preventing or treating a condition, disorder, or disease, comprising administering to a subject susceptible to or suffering from a condition, disorder or disease a provided single-stranded oligonucleotide for site-directed editing of a nucleotide (e.g. target adenosine) in a target RNA sequence, or a composition thereof. In some embodiments, a provided single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence is of a base sequence that partially or fully complementary to a portion of a transcript, which transcript is associated with a condition, disorder, or disease. In some embodiments, a base sequence is such that it preferentially binds to a transcript associated with a condition, disorder or disease over other transcripts that are not associated with said condition, disorder, or disease. In some embodiments, a condition, disorder, or disease is associated with a G to A mutation. In some embodiments, a condition, disorder, or disease is associated with a G to A mutation in SERPINA1. In some embodiments, a condition, disorder, or disease is associated with 1024 G>A (E342K) mutation in human SERPINA1. In some embodiments, a condition, disorder or disease is alpha-1 antitrypsin deficiency. In some embodiments, provided technologies increase levels, properties, and/or activities of desired products (e.g., properly folded wild-type A1AT protein in serum) and/or decreases levels, properties, and/or activities of undesired products (e.g., mutant (e.g., E342K) A1AT protein in serum), in absolute amounts (e.g., ng/mL in serum) and/or relatively (e.g., as % of total proteins or total A1AT proteins). In some embodiments, the present disclosure provides a method for increasing levels and/or activities of an alpha-1 antitrypsin (A1AT) polypeptide in the serum or blood of a subject, comprising administering to the subject an effective amount of an oligonucleotide or composition. In some embodiments, an A1AT polypeptide provides one or more higher activities compared to a reference A1AT polypeptide. In some embodiments, an A1AT polypeptide is a wild-type A1AT polypeptide. In some embodiments, method increase the amount of the A1AT polypeptide in serum. In some embodiments, a method decrease the amount of a reference A1AT polypeptide in serum. In some embodiments, a method increase the ratio of the A1AT polypeptide over a reference A1AT polypeptide in serum or blood. In some embodiments, a reference A1AT polypeptide is mutated. In some embodiments, a reference A1AT polypeptide is not properly folded. In some embodiments, a reference A1AT polypeptide is an E342K A1AT polypeptide. In some embodiments, the present disclosure provides a method for decreasing levels and/or activities of a mutant alpha-1 antitrypsin (A1AT) polypeptide in the serum or blood of a subject, comprising administering to the subject an effective amount of an oligonucleotide or composition. In some embodiments, a subject is susceptible to or suffering from a condition, disorder or disease. In some

embodiments, a condition, disorder or disease is alpha-1 antitrypsin deficiency. In some embodiments, a subject is a human. In some embodiments, a subject comprises a mutation in human SERPINA1. In some embodiments, a subject comprises 1024 G>A (E342K) mutation in human SERPINA1. In some embodiments, a subject is homozygous with respect to the mutation. In some embodiments, a subject is heterozygous with respect to a mutation.

[001024] In some embodiments, a condition, disorder or disease is not associated with a G to A mutation. In some embodiments, a condition, disorder or disease is associated with increased level and/or activity of a transcript and/or an encoded product thereby, and a provided technology can reduce level and/or activity of a transcript and/or an encoded product thereby, e.g., through introducing one or more A to I to a transcript. In some embodiments, a condition, disorder or disease is associated with decreased level and/or activity of a transcript and/or an encoded product thereby, and a provided technology can increase level and/or activity of a transcript and/or an encoded product thereby, e.g., through introducing one or more A to I to a transcript. In some embodiments, a condition, disorder or disease is associated with splicing, and a provided technology provides splicing modulation through introducing one or more A to I to a transcript (e.g., pre-mRNA).

[001025] In some embodiments, oligonucleotide compositions in provided methods are chirally controlled oligonucleotide compositions. In some embodiments, a method of treating a condition, disorder or disease can include administering a composition comprising a plurality of oligonucleotides sharing a common base sequence, which base sequence is complementary to a target sequence in a target transcript. Among other things, the present disclosure provides an improvement that comprises administering as the oligonucleotide composition a chirally controlled oligonucleotide composition as described in the present disclosure, characterized in that, when it is contacted with the target transcript in a system, adenosine editing of the transcript is improved relative to that observed under a reference condition selected from the group consisting of absence of the composition, presence of a reference composition, and any combinations thereof. In some embodiments, a reference composition is a racemic preparation of oligonucleotides of the same sequence or constitution. In some embodiments, a target transcript is an oligonucleotide transcript.

[001026] As appreciated by those skilled in the art, among other things, provided technologies can be utilized for various applications which involve and/or can benefit from an adenosine to inosine conversion. Certain applications are described in below.

Application	Application	Treatment Modality		
		oligonucleotide-mediated splicing	oligonucleotide/ siRNA-mediated silencing	RNA editing
Alter mRNA splicing	Exon skipping/inclusion/restore frame	✓		✓
Silence protein expression	Reduce levels of toxic mRNA/protein		✓	✓

Fix nonsense mutations (e.g. those that cannot be splice-corrected)	Restore protein expression			✓
Fix missense mutations (e.g., those that cannot be splice-corrected)	Restore protein function			✓
Modify amino acid codons	Alter protein level/function			✓
Remove upstream ORF	Increase protein expression			✓

[001027] Those skilled in the art reading the present disclosure will appreciate that various G to A mutations, e.g., those in transcripts from C to T mutations, a type of the most common mutations occurring in human genes, may be corrected and thus benefit from provided technologies. In some embodiments, provided technologies may be utilized to target mutations associated with various polar or charged amino acids (e.g., Ser, Tyr, Asp, Glu, His, Asn, Gln, Lys, etc.), stop codons (opal, ochre and amber), transcriptional start sites, splicing signals, microRNA recognition sites, repetitive elements, microRNAs (miRNAs), protein encoding transcripts, etc. Among other things, provided technologies can elicit diverse functional outcomes, e.g., altered splicing, restored/improved protein expression and/or functions, etc.

[001028] In some embodiments, through editing provided technology can restore protein functions (e.g., fix nonsense and missense mutations that cannot be splice-corrected, remove stop mutations, prevent protein misfolding and aggregation, etc., and can be utilized for preventing and/or treating various conditions, disorders or diseases such as recessive or dominant genetically defined diseases), modify protein functions (e.g., alter protein processing (e.g., protease cleavage sites), protein-protein interactions, modulate signaling pathways, etc., and can be utilized for preventing and/or treating various conditions, disorders or diseases such as those related to ion channel permeability), protein upregulation (e.g., miRNA target site modification, modifying upstream ORFs, modification of ubiquitination sites, etc., and can be utilized for preventing and/or treating various conditions, disorders or diseases such as Haploinsufficient diseases)). In some embodiments, a provided technology restores or improves expression, level, function and/or activity of a protein. In some embodiments, a provided technology is useful for preventing or treating a recessive or dominant genetically defined condition, disorder or disease, e.g., one associated with a G to A mutation. In some embodiments, a condition, disorder or disease is a liver condition, disorder or disease. In some embodiments, a condition, disorder or disease is a metabolic liver condition, disorder or disease. In some embodiments, a condition, disorder or disease is a neurodevelopmental condition, disorder or disease. In some embodiments, a provided technology modify express, level, function and/or activity of a protein. In some embodiments, a provided technology reduces express, level, function and/or activity of a protein. In some embodiments, a provided technology increases express, level, function and/or activity of a protein. In some embodiments, a provided technology modulate ion channel permeability. In some embodiments, a provided technology is useful for preventing or treating a condition, disorder or disease associated with ion channel permeability. In some

embodiments, a condition, disorder or disease is familial epilepsies. In some embodiments, a condition, disorder or disease is neuropathic pain. In some embodiments, a condition, disorder or disease is AATD. In some embodiments, a condition, disorder or disease is Rett syndrome. In some embodiments, a condition, disorder or disease is recessive or dominant genetically defined diseases. In some embodiments, a provided technology modifies a nucleic acid (e.g., miRNA) target site. In some embodiments, a provided technology modifies, reduces function or activity of, removes, or suppresses an upstream ORF (e.g., in some embodiments, modifies an A (e.g., of an ATG start codon of an uORF)). In some embodiments, a provided technology modifies a modification site of a protein, e.g., a ubiquitination site. In some embodiments, a provided technology is useful for preventing or treating a condition, disorder or disease associated with haploinsufficiency. In some embodiments, a provided technology is useful for preventing or treating a neuronal condition, disorder or disease. In some embodiments, a provided technology is useful for preventing or treating a neuromuscular condition, disorder or disease. In some embodiments, a provided technology is useful for preventing or treating dementias. In some embodiments, a provided technology is useful for preventing or treating dementias. In some embodiments, a provided technology is useful for preventing or treating a haploinsufficient condition, disorder or disease. In some embodiments, the provided technology provides a method for prevent or treating a condition, disorder or disease, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or a composition thereof as described herein. Those skilled in the art appreciate that through, e.g., editing a nucleobase such as A in a RNA, a protein encoded thereby can be edited. In some embodiments, an amino acid residue is replaced with another amino acid residue. In some embodiments, a protein is elongated. In some embodiments, a protein is shortened. In some embodiments, expression, level, function, stability, property and/or activity are modulated. In some embodiments, some properties and/or activities are enhanced while others are reduced or maintained the same. In some embodiments, some properties and/or activities are reduced while others are enhanced or maintained the same.

[001029] In some embodiments, provided technology edits a nucleic acid or a codon comprising a mutation. In some embodiments, a mutation is a nonsense mutation. In some embodiments, a mutation is a missense mutation. In some embodiments, a mutation is a silent mutation. In some embodiments, a provided technology fixes a nonsense mutation. In some embodiments, a provided technology fixes a missense mutation. In some embodiments, a provided technology removes a stop mutation. In some embodiments, a provided technology prevents or reduces misfolding and/or aggregation. In some embodiments, a provided technology edits a codon comprising a mutation. In some embodiments, an edited nucleobase is a mutation. In some embodiments, an edited nucleobase is not a mutation but another nucleobase in a codon. In some embodiments, after editing a codon becomes its corresponding wild type codon. In some embodiments, after editing a codon encodes the same amino acid as a wild type codon. In some embodiments, after editing a codon encodes a different amino acid from a wild type codon. In some embodiments, a protein comprising such a different amino acid residue shares one or more properties and/or performs one or more functions of its corresponding wild type protein.

In some embodiments, a protein comprising such a different amino acid residue shares more similarities to a wild type protein, and/or provides higher levels of desired activities compared to a corresponding mutated, un-edited protein. In some embodiments, a nonsense or missense mutation cannot be splice-corrected. In some embodiments, a provided technology creates a silent mutation. In some embodiments, a silent mutation modulates levels of an encoded protein. In some embodiments, a protein level is increased. In some embodiments, a protein level is decreased.

[001030] In some embodiments, a provided technology modifies protein function. In some embodiments, a provided technology changes one or more properties and/or functions of a nucleic acid (e.g., a transcript) and/or a protein. In some embodiments, a provided technology increases, promotes, or enhances one or more properties and/or functions of a nucleic acid (e.g., a transcript) and/or a protein. In some embodiments, a provided technology provide one or more new properties and/or activities, e.g., of a nucleic acid (e.g., a transcript) and/or a protein. In some embodiments, a provided technology decreases, inhibits, or removes one or more properties and/or functions of a nucleic acid (e.g., a transcript) and/or a protein. In some embodiments, a provided technology alter protein processing. For example, in some embodiments, protease cleavage sites are edited. In some embodiments, provided technologies edit one or more residues involved in protein-protein interactions. In some embodiments, provided technologies edit amino acid residues at protein-protein interactions domains. In some embodiments, through editing mRNAs that encode proteins, residues at various regions of polypeptides, e.g., protease cleavage sites, various domains (e.g., protein-protein interactions domains), modification sites, miRNA targeting sites, ubiquitination sites, etc. can be edited. In some embodiments, provided technologies modulate signaling pathways.

[001031] In some embodiments, provided technologies restore, increase or enhance levels of functional proteins. In some embodiments, provided technologies reduce levels and/or activities of mutant or undesired nucleic acids (e.g., RNA transcripts) and proteins. In some embodiments, provided technologies restore or correct expression of one or more polypeptides. In some embodiments, provided technologies can upregulate expression. In some embodiments, provided technologies can upregulate translation. In some embodiments, provided technologies can upregulate activity levels of polypeptides. In some embodiments, provided technologies modify functions of target nucleic acids (e.g., RNA transcripts) and/or products encoded thereby (e.g., polypeptides). In some embodiments, provided technologies modulate post-translation modifications of target nucleic acids (e.g., RNA transcripts) and/or products encoded thereby (e.g., polypeptides). In some embodiments, provided technologies can upregulate levels of polypeptides. In some embodiments, provided technologies edit codons encoding amino acid residues involved in protein-protein interactions or protein interactions with other agents, including in some embodiments, changing the amino acid residues to different amino acid residues to enhance or reduce interactions. In some embodiments, provided technologies modify one or more functions of nucleic acids and/or proteins. In some embodiments, provided technologies can modulate protein-protein interactions. In some embodiments, provided technologies edit encoding transcripts to remove, change, or incorporate amino acid residues for post-translation modification. In some

embodiments, provided technologies modulate post-translational modifications. In some embodiments, provided technologies modulate nucleic acid folding. In some embodiments, provided technologies modulate protein folding. In some embodiments, provided technologies modulate stability of transcripts and/or products thereof. In some embodiments, provided technologies modulate protein stability. In some embodiments, provided technologies modulate processing of transcripts and/or products thereof. In some embodiments, provided technologies modulate nucleic acids (e.g., transcripts) processing. In some embodiments, provided technologies alter protein processing. In some embodiments, provided technologies modulate post translational processes. For example, in some embodiments, provided technologies modulate PCSK9 post translational processes. Among other things, provided technologies are applicable to a wide range of therapeutic applications with large patient populations.

[001032] For example, as demonstrated herein, in some embodiments, one or more amino acid residues of one or more proteins may be changed through editing of encoding mRNAs to modulate protein-protein interactions. Suitable amino acid residues for editing include various reported amino acid residues involved in protein-protein interactions, or can be identified through technologies available in the art, e.g., mutation technologies, structural biology technologies, etc. In some embodiments, the present disclosure provides technologies for modulating levels, properties and/or activities of nucleic acids (e.g., transcripts) and/or proteins through editing of nucleic acids (e.g., transcripts) and/or proteins that interact them. In some embodiments, the present disclosure provides technologies for modulating levels and/or activities of a protein (e.g., a transcription factor) and/or transcription and/or expression regulated thereby. In some embodiments, a provided technology comprises editing an amino acid residue of a protein (e.g., a transcription factor) or a partner protein that it interacts with, wherein interaction between the protein and a partner protein is reduced or enhanced. In some embodiments, a provided technology comprises editing an amino acid residue of a protein (e.g., a transcription factor) or a partner protein that it interacts with, wherein interaction between the protein and a partner protein is reduced. In some embodiments, such editing stabilizes a protein so that its levels and/or activities (e.g., transcription activation of certain nucleic acids) are increased. In some embodiments, the present disclosure provides technologies for modulating (e.g., activating, increasing, reducing, suppressing, etc.) expression of a nucleic acid, comprising editing an adenosine in a transcript encoding a protein that regulates expression of the nucleic acid, or a protein that interacts with a protein that regulates expression of the nucleic acid, or a protein that is a member of a pathway comprising a protein that regulates expression of the nucleic acid, wherein editing modulates levels and/or activities of a protein that regulates expression of the nucleic acid. In some embodiments, transcripts levels and/or activities of a nucleic acids are modulated. In some embodiments, levels and/or activities of proteins encoded by such transcripts are modulated. Among other things, the present disclosure confirms that many functions, activities, pathways, etc., that involve protein-protein interactions may be modulated through editing of interacting amino acid residues of one or more interacting proteins. For example, editing of one or more amino acid residues in NRF2 (e.g., Glu82 (e.g., to Gly), Glu79 (e.g., to Gly), Glu78 (e.g., to Gly), Asp76 (e.g., to Gly), Ile28 (to Val), Asp27

(e.g., to Gly), Gln26 (e.g., to Arg), etc.) or Keap1 (e.g., Ser603 (e.g., to Gly), Tyr572 (e.g., to Cys), Tyr525 (e.g., to Cys), Ser508 (e.g., to Gly), His436 (e.g., to Arg), Asn382 (e.g., to Asp), Arg380 (e.g., to Gly), Tyr334 (e.g., to Cys), etc.) can increase levels and/or activities of NRF2, and/or expression of various nucleic acids (e.g., various genes) regulated byNRF2. In some embodiments, the present disclosure provides a method for modulating, e.g., reducing, NRF2-Keap1 interaction in a system, comprising administering to a system comprising a NRF2 or Keap1 mRNA an oligonucleotide or a composition thereof, wherein the oligonucleotide edits an adenosine in the mRNA so that an amino acid residue in a protein encoded by the mRNA is edited to be a different residue. In some embodiments, the present disclosure provides a method for increasing a level and/or activity of NRF2 in a system, comprising administering to a system comprising a NRF2 or Keap1 mRNA an oligonucleotide or a composition thereof, wherein the oligonucleotide edits an adenosine in the mRNA so that an amino acid residue in a protein encoded by the mRNA is edited to be a different residue. In some embodiments, the present disclosure provides a method for increasing transcription or expresson of a NRF2-regulated nucleic acid (e.g., a gene), comprising administering to a system comprising a NRF2 or Keap1 mRNA an oligonucleotide or a composition thereof, wherein the oligonucleotide edits an adenosine in the mRNA so that an amino acid residue in a protein encoded by the mRNA is edited to be a different residue. In some embodiments, levels and/or activities of transcripts from NRF2-regulated nucleic acids, e.g., genes such as SRGN, HMOX1,SLC7a11, NQO1, etc., and/or products (e.g., proteins) encoded thereby are increased. In some embodiments, a system comprising a NRF2 and a Keap1 mRNA, and NRF2 and Keap1 proteins are translated from such mRNA. In some embodiments, a target adenosine of a NRF2 and/or a Keap1 mRNA is edited so that an amino acid residue is replaced with a different amino acid residue after translation. In some embodiments, an administered oligonucleotide or composition thereof targets NRF2 mRNA. In some embodiments, an administered oligonucleotide or composition thereof targets Keap1 mRNA. In some embodiments, an amino acid residue in NRF2 (e.g., Glu82 (e.g., to Gly), Glu79 (e.g., to Gly), Glu78 (e.g., to Gly), Asp76 (e.g., to Gly), Ile28 (to Val), Asp27 (e.g., to Gly), Gln26 (e.g., to Arg), etc.) is edited. In some embodiments, an amino acid residue in Keap1 (e.g., Ser603 (e.g., to Gly), Tyr572 (e.g., to Cys), Tyr525 (e.g., to Cys), Ser508 (e.g., to Gly), His436 (e.g., to Arg), Asn382 (e.g., to Asp), Arg380 (e.g., to Gly), Tyr334 (e.g., to Cys), etc.) is edited. In some embodiments, two or more amino acid residues are edited. In some embodiments, each edited amino acid residue is independently a NRF2 residue. In some embodiments, each edited amino acid residue is independently a Keap1 residue. In some embodiments, an edited amino acid residue is a Keap1 residue, and an edited amino acid residue is a NRF2 residue. In some embodiments, a system is or comprises a cell. In some embodiments, a systeim is or comprises a tissue. In some embodiments, a system is or comprises an organ. In some embodiments, a system is an orgasm. In some embodiments, a system is an in vitro system. Certain NRF2-targeting and Keap1-targeting oligonucleotides and/or oligonucleotide compositions are presented in the Table(s) as examples. In some embodiments, provided technologies are useful for treating a condition, disorder or disease related to NRF2. In some embodiments, provided technologies are useful for treating a condition, disorder or disease related to Keap1. In some

embodiments, provided technologies are useful for treating a condition, disorder or disease related toNRF2-Keap1 interaction.

[001033] In some embodiments, provided technologies modulate enzymatic activities. In some embodiments, provided technologies increase an enzymatic activity, e.g., through editing a codon to a codon encoding a amino acid residue that can increase an enzymatic activity. In some embodiments, provided technologies decrease an enzymatic activity, e.g., those associated with a condition, disorder or disease, through editing a codon to a codon encoding a amino acid residue that can decrease an enzymatic activity. Various enzymatic activities, in many cases with amino acid residues involved for such activities, are reported or can be identified and characterized, and can be modulated in accordance with the present disclosure. In some embodiments, an activity is a kinase activity.

[001034] In some embodiments, editing of a protein (e.g., through editing of its encoding mRNA to change one or more amino acid residues) decreases degradation of the protein or a protein which it interacts with. In some embodiments, editing of a protein upregulate its levels. In some embodiments, editing of a protein modulate protein processing. In some embodiments, editing of a protein modulate its folding. In some embodiments, editing of a protein modulate its stability. In some embodiments, editing of a protein modulate protein modification (e.g., increasing, decreasing, removing or introducing a modification site, etc.). In some embodiments, editing of a protein modulate post-translational modification (e.g., increasing, decreasing, removing or introducing a modification site, etc.). In some embodiments, provided technologies are useful for treating associated conditions, disorders or diseases, such as dementias, familial epilepsies, neuropathic pain, neuromuscular disorders, dementias, haploinsufficient diseases, loss of function conditions, disorders or diseases, etc.

[001035] Technologies of present disclosure can provide efficient editing in various types of cells, tissues, organs and/or organisms. In some embodiments, provided technologies can provide efficient editing in various immune cells. As demonstrated herein, provided technologies can provide high levels of editing in human peripheral blood mononuclear cells (PBMCs). Among other things, provided technologies can provide high levels of editing in various cell populations such as CD4+ T cells, CD8+ T cells, CD14 monocytes, CD19 B cells, NK cells, Tregs T cells, etc. In some embodiments, immune cells are activated (e.g., by PHA) before contact with oligonucleotides. In some embodiments, cells are non-activated. In some embodiments, similar levels of editing are observed in activated and non-activated cells. In some embodiments, higher levels of editing are observed in activated cells. In some embodiments, after editing cells, e.g., PBMCs, may be sorted into various cell types. In some embodiments, cells can be first sorted before contact with oligonucleotides. As appreciated by those skilled in the art, immune cells have a number of functions and may be utilized for a number of purposes including for treating various conditions, disorders or diseases. In some embodiments, immune cells are utilized in immunotherapy, e.g., for various types of cancer. Among other things, the present disclosure provides technologies for editing one or more transcripts expressed in immune cells to improve its properties and/or activities for immunotherapy. In some embodiments, provided technologies can reduce

expression and/or activity of one or more genes in immune cells, e.g., FAS, BID, CTLA4, PDCD1, CBLB, PTPN6, TRAC, TRBC, etc. In some embodiments, transcripts from such genes are edited. In some embodiments, a target cell is a T cell, e.g., a CD8+ T cell (e.g., a CD8+ naïve T cell, central memory T cell, or effector memory T cell), a CD4+ T cell, a natural killer T cell (NK T cell), a regulatory T cell (Treg), a stem cell memory T cell, a lymphoid progenitor cell, a hematopoietic stem cell, a natural killer cell (NK cell) or a dendritic cell. In some embodiments, cells are CD4+ cells, e.g., CD4+ T cells. In some embodiments, cells are CD8+ cells, e.g., CD8+ T cells. In some embodiments, cells are CD14+ cells, e.g., CD14+ monocytes. In some embodiments, cells are CD19+ cells, e.g., CD19+ B cells. In some embodiments, cells are NC cells. In some embodiments, cells are T-regulatory cells. In some embodiments, a target cell is an induced pluripotent stem (iPS) cell or a cell derived from an iPS cell, e.g., an iPS cell generated from a subject, manipulated to alter (e.g., induce a mutation in) expression of one or more genes, e.g., FAS, BID, CTLA4, PDCD1, CBLB, PTPN6, TRAC or TRBC gene, and differentiated into, e.g., a T cell, e.g., a CD8+ T cell (e.g., a CD8+ naïve T cell, central memory T cell, or effector memory T cell), a CD4+ T cell, a stem cell memory T cell, a lymphoid progenitor cell or a hematopoietic stem cell.

[001036] Among other things, provided technologies are useful for increasing, enhancing, improving or upregulating levels, properties, activities, etc., of various polypeptides including various proteins. In some embodiments, provided technologies modify binding or target sites, e.g., miRNA target sites. In some embodiments, provided technologies modify regulatory elements in transcripts. In some embodiments, provided technologies modify upstream ORFs (e.g., A in ATG). In some embodiments, provided technologies modify amino acid residues that can be modified, e.g., ubiquitination sites. Those skilled in the art appreciate provided technologies can also be useful for decreasing or downregulating levels, properties, activities, etc., of various polypeptides including various proteins through modifying RNAs.

[001037] In some embodiments, an editing site, e.g., a target adenosine, is in a coding region. In some embodiments, it is in a non-coding region. In some embodiments, a target nucleic acid is a non-coding RNA.

[001038] Certain applications are described, e.g., in WO 2016/097212, WO 2017/220751, WO 2018/041973, WO 2018/134301A1, WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376.

[001039] Many adenosines associated with various conditions, disorders or diseases are reported or can be identified, and can be targeted using provided technologies, e.g., for preventing or treating associated conditions, disorders or diseases. For example, it has been reported that various adenosines associated with various conditions, disorders or diseases have been identified in SNCA (e.g., Parkinson's disease), APP (e.g., Alzheimer's Disease), Tau (e.g., Alzheimer's Disease), Nav1.7 (e.g., Chronic Pain), C9orf72 (e.g., Amyotrophic Lateral Sclerosis), SOD1 (e.g., Amyotrophic Lateral Sclerosis), DYRK1A (e.g., Down Syndrome), IT15 (e.g., Huntington's Disease), HEXA (e.g., Tay-Sachs Disease), RAI1 (e.g., Protocki-Lupski Syndrome), ABCA4 (e.g., Stargardt Disease), USH2A (e.g., Usher Syndrome), NRP1 (e.g., Wet AMD, Dry AMD, etc.), PCSK9 (e.g., cardiovascular conditions, disorders or diseases), LIPA (e.g., Cholesteryl Ester

Storage Disease), HFE (e.g., Hemochromatosis), ALAS1 (e.g., Porphyria/Acute Hepatic Porphyria), ATP7B (Wilson Disease), COL4A5 (e.g., Alport Syndrome), LDHA (e.g., Primary Hyperoxaluria), HAO1 (e.g., Primary Hyperoxaluria Type 2), DUX4 (e.g., Facioscapulohumeral Dystrophy), DMPK (e.g., Myotonic Dystrophy), BCL11A (e.g., Sickle Cell Disease), Mex3B (e.g., Asthma), CIDEC (e.g., obesity), SCD1 (e.g., obesity), GNB3 (e.g., obesity), FGFR3 (e.g., Achondroplasia), CLCN7 (e.g., Osteopetrosis), PMP22 (e.g., Charcot-Marie-Tooth Disease), ENAC (e.g., Cystic Fibrosis), GHR (e.g., Acromegaly), TTR (e.g., Transthyretin Amyloidosis (familial)), etc. In some embodiments, the present disclosure provides oligonucleotides and compositions targeting such adenosines, and methods for preventing or treating such conditions, disorders or diseases.

[001040] In some embodiments, conditions, disorders or diseases that may be treated include, for example, , alpha-1 antitrypsin deficiency, Alzheimer's disease, amyloid diseases, Becker muscular dystrophy, breast cancer predisposition mutations, Canavan disease, Charcot-Marie-Tooth disease, cystic fibrosis, Factor V Leiden deficiency, Type 1 diabetes, Type 2 diabetes, Duchenne muscular dystrophy, Fabry disease, hereditary tyrosinemia type I (HTI), familial adenomatous polyposis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, familial dysautonomia, familial hypercholesterolemia, Friedreich's ataxia, Gaucher disease type I, Gaucher disease II, glycogen storage disease type II, GM2 gangliosidosis, hemochromatosis, hemophilia A, hemophilia B, hemophilia C, hexosaminidase A deficiency, ovarian cancer predisposition mutations, obesity, phenylketonuria, polycystic kidney disease, prion disease, senile systemic amyloidosis, sickle-cell disease, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, Wilson's disease, Parkinson's disease, and hereditary blindness. In some embodiments, diseases/targets include: cystic fibrosis transmembrane conductance regulator gene (CFTR); albinism, Amyotrophic lateral sclerosis, Asthma, β-thalassemia, Cadasil syndrome , Chronic Obstructive Pulmonary Disease (COPD), Distal Spinal Muscular Atrophy (DSMA), Duchenne/Becker muscular dystrophy, Dystrophic Epidermolysis bullosa, Epidermylosis bullosa, dystrophin gene (DMD); amyloid beta (A4) precursor protein gene (APP); Factor V Leiden associated disorders, Glucose-6-phosphate dehydrogenase, Haemophilia, Hereditary Hematochromatosis, Hunter Syndrome, Huntington's disease, Hurler Syndrome, Inflammatory Bowel Disease (IBD), Inherited polyagglutination syndrome, Leber congenital amaurosis, Lesch-Nyhan syndrome, Lynch syndrome, Marfan syndrome, Mucopolysaccharidosis, Myotonic dystrophy types I and II, neurofibromatosis, Niemann-Pick disease type A, B and C, NY-eso1 related cancer, Rett syndrome, NY-ESO-1 related cancer, 11-thalassemia , Galactosemia, Gaucher's Disease, Factor XII gene; Factor IX gene; Factor XI gene; HgbS; insulin receptor gene; adenosine deaminase gene; alpha-1 antitrypsin gene; breast cancer 1 gene (BRCA1); breast cancer 2 gene (BRCA2); aspartocyclase gene (ASPA); galactosidase alpha gene (GLA); adenomatous polyposis coli gene (APC); inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP); glucosidase beta acid gene (GBA); glucosidase alpha acid gene (GAA); hemochromatosis gene (HFE); apolipoprotein B gene (APOB); low density lipoprotein receptor gene (LDLR), low density lipoprotein receptor adaptor protein 1 gene (LDLRAP1); proprotein convertase subtilisin/kexin type 9 gene (PCSK9);

polycystic kidney disease 1 (autosomal dominant) gene (PKD-1); Prion protein gene (PRNP); PTP-1B; 7-dehydrocholesterol reductase gene (DHCR7); survival of motor neuron 1, telomeric gene (SMN1); biquitin-like modifier activating enzyme 1 gene (UBA1); dynein, cytoplasmic 1, heavy chain 1 gene (DYNC1H1), survival of motor neuron 2, centromeric gene (SMN2); (vesicle-associated membrane protein)-associated protein B and C (VAPB); hexosaminidase A (alpha polypeptide) gene (HEXA); transthyretin gene (TTR); ATPase, Cu++ transporting, beta polypeptide gene (ATP7B); phenylalanine hydroxylase gene (PAH); rhodopsin gene; retinitis pigmentosa 1 (autosomal dominant) gene (RP1); retinitis pigmentosa 2 (X-linked recessive) gene (RP2), Sturge-Weber Syndrome, Parkinson's disease, Peutz-Jeghers Syndrome, Pompe's disease, Primary Ciliary Disease, Prothrombin mutation related disorders, such as the Prothrombin G20210A mutation, Pulmonary Hypertension, Sandhoff Disease, Severe Combined Immune Deficiency Syndrome (SCID), Stargardt's Disease, Tay-Sachs Disease, Usher syndrome, X-linked immunodeficiency, various forms of cancer (e.g. BRCA1 and 2 linked breast cancer and ovarian cancer), and the like and other known gene targets. Other diseases include those point mutations or small deletions or insertions or diseases that can be corrected by point changes or small deletions or insertions listed in http://www.omim.org/ Online Mendelian Inheritance in Man® An Online Catalog of Human Genes and Genetic Disorders Updated, e.g., on 24 September 2021.

[001041] In some embodiments, the present disclosure provides technologies targeting IDUA. In some embodiments, the present disclosure provides methods for preventing or treating a condition, disorder or disease associated with IDUA, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition. In some embodiments, a subject benefits from a G to A editing in IDUA. In some embodiments, a condition, disorder or disease is Hurler syndrome. In some embodiments, the present disclosure provides technologies targeting PINK1. In some embodiments, the present disclosure provides methods for preventing or treating a PINK1-associated condition, disorder or disease, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition. In some embodiments, a subject benefits from a G to A editing in PINK1. In some embodiments, a condition, disorder or disease is Parkinson's disease. In some embodiments, the present disclosure provides technologies targeting Factor V Leiden. In some embodiments, the present disclosure provides methods for preventing or treating a Factor V Leiden-associated condition, disorder or disease, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition. In some embodiments, a subject benefits from a G to A editing in Factor V Leiden. In some embodiments, a condition, disorder or disease is Factor V Leiden deficiency. In some embodiments, the present disclosure provides technologies targeting CFTR. In some embodiments, the present disclosure provides methods for preventing or treating a CFTR-associated condition, disorder or disease, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition. In some embodiments, a subject benefits from a G to A editing in CFTR. In some embodiments, a condition, disorder or disease is cystic fibrosis.

[001042] It is reported that there are over 32,000 pathogenic human SNPs nearly half of which are G to A mutations that can be corrected by provided technologies. Indeed, tens of thousands of disease are reported to be associated with G to A mutation and can be prevented or treated by provided technologies. Among other things, provided technologies can be utilized to prevent or treat many conditions, disorders or diseases associated with premature stop codons; it is reported that ~12% of all reported disease-causing mutations are single point mutations that result in a premature stop codon. In some embodiments, the provided technologies correct a premature stop codon. See, e.g., ClinVar database; Gaudelli NM et al., Nature. 2017 Nov 23; 551(7681): 464–471; Keeling KM et al., Madame Curie Bioscience Database 2000-2013; etc.

[001043] In some embodiments, when an oligonucleotide or oligonucleotide composition is contacted with a target nucleic acid comprising a target adenosine in a system, a target adenosine in a target nucleic acid is modified. In some embodiments, when an oligonucleotide or oligonucleotide composition is contacted with a target nucleic acid comprising a target adenosine in a system, level of a target nucleic acid is reduced compared to absence of the product or presence of a reference oligonucleotide. In some embodiments, when an oligonucleotide or oligonucleotide composition is contacted with a target nucleic acid comprising a target adenosine in a system, splicing of a target nucleic acid or a product thereof is altered compared to absence of the oligonucleotide or presence of a reference oligonucleotide. In some embodiments, when an oligonucleotide or oligonucleotide composition is contacted with a target nucleic acid comprising a target adenosine in a system, level of a product of a target nucleic acid is altered compared to absence of the product or presence of a reference oligonucleotide. In some embodiments, level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to a target nucleic acid but a target adenosine is modified. In some embodiments, level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to a target nucleic acid but a target adenosine is replaced with inosine. In some embodiments, level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to a target nucleic acid but the adenine of a target adenosine is replaced with guanine. In some embodiments, a product is a protein. In some embodiments, a target adenosine is a mutation from guanine. In some embodiments, a target adenosine is more associated with a condition, disorder or disease than a guanine at the same position. In some embodiments, an oligonucleotide is capable of forming a double-stranded complex with a target nucleic acid. In some embodiments, a target nucleic acid or a portion thereof is or comprises RNA. In some embodiments, a target adenosine is of an RNA. In some embodiments, a target adenosine is modified, and the modification is or comprises deamination of a target adenosine. In some embodiments, a target adenosine is modified and the modification is or comprises conversion of a target adenosine to an inosine. In some embodiments, a modification is promoted by an ADAR protein. In some embodiments, a system is an *in vitro* or *ex vivo* system comprising an ADAR protein. In some embodiments, a system is or comprises a cell that comprises or expresses an ADAR protein. In some embodiments, a system is a subject comprising a cell that comprises or expresses an ADAR protein. In some embodiments, a ADAR protein is ADAR1. In some embodiments, an ADAR1 protein is or comprises p110 isoform. In some

embodiments, an ADAR1 protein is or comprises p150 isoform. In some embodiments, an ADAR1 protein is or comprises p110 and p150 isoform. In some embodiments, a ADAR protein is ADAR2. As demonstrated herein, the present disclosure among other things provides technologies for recruiting enzymes to target sites (e.g., those comprising target As), comprising contacting such target sites with, or administering to systems comprising or expressing polynucleotide (e.g., RNA) comprising such target sites, provided oligonucleotides or compositions thereof. In some embodiments, an enzyme is an RNA-editing enzyme such as ADAR1, ADAR2, etc. as described herein.

[001044] In some embodiments, an oligonucleotide composition comprising a plurality of oligonucleotides provide a greater level, e.g., a target adenosine is modified at a greater level, than that is observed with a comparable reference oligonucleotide composition. In some embodiments, a reference oligonucleotide composition comprises no or a lower level of oligonucleotides of the plurality. In some embodiments, a reference composition does not contain oligonucleotides that have the same constitution as an oligonucleotide of the plurality. In some embodiments, a reference composition does not contain oligonucleotides that have the same structure as an oligonucleotide of the plurality. In some embodiments, a reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of 2'-F modifications compared to oligonucleotides of the plurality. In some embodiments, a reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of 2'-OMe modifications compared to oligonucleotides of the plurality. In some embodiments, a reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality have a different sugar modification pattern compared to oligonucleotides of the plurality. In some embodiments, a reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of modified internucleotidic linkages compared to oligonucleotides of the plurality. In some embodiments, a reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of phosphorothioate internucleotidic linkages compared to oligonucleotides of the plurality. In some embodiments, a composition is a stereorandom oligonucleotide composition. In some embodiments, a reference composition is a stereorandom oligonucleotide composition of oligonucleotides of the same constitution as oligonucleotides of the plurality.

[001045] In some embodiments, the present disclosure provides technologies for modifying a target adenosine in a target nucleic acid, comprising contacting a target nucleic acid with an provided oligonucleotide or oligonucleotide composition as described herein. In some embodiments, the present disclosure provides a method for deaminating a target adenosine in a target nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition as described herein. In some embodiments, the present disclosure provides a method for producing, or restoring or increasing level of a product of a particular nucleic acid, comprising contacting a target nucleic acid with a provided oligonucleotide or composition wherein a target

nucleic acid comprises a target adenosine, and the particular nucleic acid differs from a target nucleic acid in that the particular nucleic acid has an I or G instead of a target adenosine. In some embodiments, the present disclosure provides a method for reducing level of a product of a target nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition of the present disclosure, wherein a target nucleic acid comprises a target adenosine. In some embodiments, a product is a protein. In some embodiments, a product is a mRNA.

[001046] In some embodiments, the present disclosure provides a method, comprising:

contacting an oligonucleotide or composition with a sample comprising a target nucleic acid and an adenosine deaminase, wherein:

the base sequence of the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of a target nucleic acid; and

a target nucleic acid comprises a target adenosine;

wherein a target adenosine is modified.

[001047] In some embodiments, the present disclosure provides a method comprising:

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

[001048] In some embodiments, the present disclosure provides a method comprising:

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of a target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality.

[001049] In some embodiments, the present disclosure provides a method comprising:

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

[001050] In some embodiments, the present disclosure provides a method comprising:

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of a target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides

sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality.

[001051] In some embodiments, the present disclosure provides a method comprising:

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition); and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

[001052] In some embodiments, the present disclosure provides a method comprising:

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of a target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising a target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of a target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic

linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition).

[001053] In some embodiments, a first oligonucleotide composition is an oligonucleotide composition as described herein. In some embodiments, a first oligonucleotide composition is a chirally controlled oligonucleotide composition. In some embodiments, a deaminase is an ADAR enzyme. In some embodiments, a deaminase is ADAR1. In some embodiments, a deaminase is ADAR2. In some embodiments, a sample is or comprise a cell. In some embodiments, a target nucleic acid is more associated with a condition, disorder or disease, or decrease of a desired property or function, or increase of an undesired property or function, compared to a nucleic acid which differs from a target nucleic acid in that it has an I or G at the position of a target adenosine instead of a target adenosine. In some embodiments, a target adenosine is a G to A mutation.

[001054] Among other things, oligonucleotide designs of the present disclosure, e.g., nucleobase, sugar, internucleotidic linkage modifications, control of linkage phosphorus stereochemistry, and/or patterns thereof, can be applied to improve prior technologies. In some embodiments, the present disclosure provides improvement over prior technologies by introducing one or more structural features of the present disclosure, e.g., nucleobase, sugar, internucleotidic linkage modifications, control of linkage phosphorus stereochemistry, and/or patterns thereof to oligonucleotides in prior technologies. In some embodiments, an improvement is or comprises improvement from control of linkage phosphorus stereochemistry.

[001055] In some embodiments, the present disclosure provides technologies for improving adenosine editing by a polypeptide, e.g., ADAR1, ADAR2, etc., comprising incorporating into an oligonucleotide a design (e.g., one or more modifications and/or patterns thereof) as described herein. In some embodiments, a design is or comprises a modified base as described herein, e.g., at the position opposite to a target adenosine and/or one or both of its neighboring positions. In some embodiments, a design is or comprises one or more sugar modifications and/or patterns thereof, one or more base modifications and/or patterns thereof, one or more modified internucleotidic linkages and/or patterns thereof, and/or controlled stereochemistry at one or more positions and/or patterns thereof. In some embodiments, a provided technology improves editing by ADAR1 more than ADAR2. In some embodiments, a provided technology improves editing by ADAR2 more than ADAR1. In some embodiments, a provided technology improves editing by ADAR1 p110 more than p150 (e.g., in some embodiments, *R*p (e.g., of phosphorothioate internucleotidic linkages) at one or more positions). In some embodiments, a provided technology improves editing by ADAR1 p150 more than p110.

[001056] In some embodiments, a provided technology comprises increasing levels of an adenosine editing polypeptide, e.g., ADAR1 (p110 or p150) or ADAR2, or a portion thereof. In some embodiments, an increase is through expression of an exogenous of a polypeptide.

[001057] In some embodiments, a provided oligonucleotide or oligonucleotide composition does not cause significant degradation of a nucleic acid (e.g., no more than about 5%-100% (e.g., no more than about 10%-

100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.)). In some embodiments, a composition does not cause significant undesired exon skipping or altered exon inclusion in a target nucleic acid (e.g., no more than about 5%-100% (e.g., no more than about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.)).

[001058] In some embodiments, provided technologies can provide high levels of adenosine editing (e.g., conversion to inosine). In some embodiments, percentage of target adenosine editing is about 10%-100%, e.g., at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95%. In some embodiments, it is at least 10%. In some embodiments, it is at least 15%. In some embodiments, it is at least 20%. In some embodiments, it is at least 25%. In some embodiments, it is at least 30%. In some embodiments, it is at least 35%. In some embodiments, it is at least 40%. In some embodiments, it is at least 45%. In some embodiments, it is at least 50%. In some embodiments, it is at least 60%. In some embodiments, it is at least 70%. In some embodiments, it is at least 75%. In some embodiments, it is at least 80%. In some embodiments, it is at least 85%. In some embodiments, it is at least 90%. In some embodiments, it is at least 95%. In some embodiments, it is at least about 100%.

[001059] In some embodiments, an oligonucleotide or a composition thereof is capable of mediating a decrease in the expression or level of a target nucleic acid or a product thereof (e.g., by modifying a target adenosine into inosine). In some embodiments, an oligonucleotide or a composition thereof is capable of mediating a decrease in the expression or level of a target gene or a gene product thereof (e.g., by modifying a target adenosine into inosine) in a cell in vitro. In some embodiments, expression or level can be decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95%. In some embodiments, expression or level of a target gene or a gene product thereof can be decreased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95% by ADAR-mediated deamination directed by an oligonucleotide or a composition thereof, e.g., at a concentration of 10 uM or less in a cell(s) in vitro. In some embodiments, an oligonucleotide or a composition thereof is capable of provide suitable levels of activities at a concentration of 1 nM, 5 nM, 10 nM or less (e.g., when assayed in cells in vitro or in vivo).

[001060] In some embodiments, activity of provided oligonucleotides and compositions may be assessed by IC50, which is the inhibitory concentration to decrease level of a target nucleic acid or a product thereof

by 50% in a suitable condition, e.g., cell-based in vitro assays. In some embodiments, provided oligonucleotides or compositions have an IC50 no more than 0.001, 0.01, 0.1, 0.5, 1, 2, 5, 10, 50, 100, 200, 500 or 1000 nM, e.g., when assessed in cell-based assays. In some embodiments, an IC50 is no more than about 500 nM. In some embodiments, an IC50 is no more than about 200 nM. In some embodiments, an IC50 is no more than about 100 nM. In some embodiments, an IC50 is no more than about 50 nM. In some embodiments, an IC50 is no more than about 25 nM. In some embodiments, an IC50 is no more than about 10 nM. In some embodiments, an IC50 is no more than about 5 nM. In some embodiments, an IC50 is no more than about 2 nM. In some embodiments, an IC50 is no more than about 1 nM. In some embodiments, an IC50 is no more than about 0.5 nM.

[001061] In some embodiments, provided technologies can provide selective editing of target adenosine over other adenosine residues in a target adenosine. In some embodiments, selectivity of a target adenosine over a non-target adenosine is at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 fold or more (e.g., as measured by level of editing of a target adenosine over a non-target adenosine at a suitable condition, or by oligonucleotide concentrations for a certain level of editing (e.g., 0.5%, 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, etc.). In some embodiments, a selectivity is at least 2 fold. In some embodiments, a selectivity is at least 3 fold. In some embodiments, a selectivity is at least 4 fold. In some embodiments, a selectivity is at least 5 fold. In some embodiments, a selectivity is at least 10 fold. In some embodiments, a selectivity is at least 25 fold. In some embodiments, a selectivity is at least 50 fold. In some embodiments, a selectivity is at least 100 fold.

[001062] In some embodiments, the present disclosure provides a method for suppression of a transcript from a target nucleic acid sequence for which one or more similar nucleic acid sequences exist within a population, each of the target and similar sequences contains a specific characteristic sequence element that defines the target sequence relative to the similar sequences, the method comprising contacting a sample comprising transcripts of target nucleic acid sequence with an oligonucleotide , or a composition comprising a plurality of oligonucleotides sharing a common base sequence, wherein the base sequence of the oligonucleotide, or the common base sequence of the plurality of oligonucleotide, is or comprises a sequence that is complementary to the characteristic sequence element that defines the target nucleic acid sequence. In some embodiments, wherein when the oligonucleotide, or the oligonucleotide composition, is contacted with a system comprising transcripts of both the target nucleic acid sequence and a similar nucleic acid sequences, transcripts of the target nucleic acid sequence are suppressed at a greater level than a level of suppression observed for a similar nucleic acid sequence. In some embodiments, suppression of the transcripts of the target nucleic acid sequence can be 1.1-100, 2-100, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, or 10-fold greater than suppression observed for a similar nucleic acid sequence. In some embodiments, a target nucleic acid sequence is associated with (or more associated with compared to a similar nucleic acid sequence) a condition, disorder or disease. As those skilled in the art will appreciate, selective reduction of a transcript (and/or products thereof) associated with conditions, disorders or diseases, while maintaining transcripts that are not, or are less,

associated with conditions, disorders or diseases can provide a number of advantages, for example, providing disease treatment and/or prevention while maintaining one or more desired biological functions (which may provide, among other things, fewer or less severe side effects).

[001063] In some embodiments, as demonstrated herein, selectivity is at least 10 fold, or 20, 30, 40, or 50 fold or more in a system, *e.g.* a reporter assay described herein. In some embodiments, an oligonucleotide or composition can effectively reduce levels of mutant protein (*e.g.*, at least 50%, 60%, 70% or more reduction of a mutant protein) while maintaining levels of wild-type protein (*e.g.* at least 70%, 75%, 80%, 85%, 90%, 95%, or more wild-type protein remaining) in a system . In some embodiments, provided oligonucleotides are stable in various biological systems, *e.g.* in mouse brain homogenates (*e.g.*, at least 70%, 75%, 80%, 85%, 90%, 95%, or more remaining after 1, 2, 3, 4, 5, 6, 7, or 8 days). In some embodiments, provided oligonucleotides are of low toxicity. In some embodiments, provided oligonucleotides and compositions thereof, *e.g.*, chirally controlled oligonucleotides and compositions thereof, do not significant activate TLR9 (*e.g.*, when compared to reference oligonucleotides and compositions thereof (*e.g.*, corresponding stereorandom oligonucleotides and compositions thereof)). In some embodiments, provided oligonucleotides and compositions thereof, *e.g.*, chirally controlled oligonucleotides and compositions thereof, do not significantly induce complement activation (*e.g.*, when compared to reference oligonucleotides and compositions thereof (*e.g.*, corresponding stereorandom oligonucleotides and compositions thereof)).

[001064] For various applications, provided oligonucleotides and/or compositions may be provided as pharmaceutical compositions. In some embodiments, the present disclosure provides a pharmaceutical composition which comprises or delivers an effective amount of an oligonucleotide or a pharmaceutically acceptable salt thereof. In some embodiments, a pharmaceutical composition may comprise various forms of an oligonucleotide, e.g., acid, base and various pharmaceutically acceptable salt forms. In some embodiments, a pharmaceutically acceptable salt is sodium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a pharmaceutically acceptable salt is a amine salt (e.g., of an amine having the structure of $N(R)_3$). In some embodiments, a pharmaceutical composition further comprises a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition is or comprises a liquid solution. In some embodiments, a liquid composition has a controlled pH range, e.g., around or being physiological pH. In some embodiments, a pharmaceutical composition comprises or is formulated as a solution in a physiologically compatible buffers such as Hanks's solution, Ringer's solution, cerebral spinal fluid , artificial cerebral spinal fluid (aCSF) or physiological saline buffer. In some embodiments, a pharmaceutical composition comprises or is formulated as a solution in artificial cerebral spinal fluid (aCSF). In some embodiments, a pharmaceutical composition is an injectable suspension or solution. In certain embodiments, injectable suspensions or solutions are prepared using appropriate liquid carriers, suspending agents and the like. Pharmaceutical compositions can be administered in various suitable routes. In some embodiments, pharmaceutical compositions are formulated for oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and

systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous, intrathecal, intracerebroventricular or epidural injection as, for example, a sterile solution or suspension, e.g., in physiologically compatible buffers such as Hanks's solution, Ringer's solution, artificial cerebral spinal fluid (aCSF) or physiological saline buffer or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[001065] Among other things, the present disclosure provides technologies for preventing or treating conditions, disorders or diseases. In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition as described herein. In some embodiments, a condition, disorder or disease is amenable to (e.g., can benefit from) A to I conversion. In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease associated with a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition as described herein. In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease amenable to a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition as described herein. In some embodiments, the present disclosure provides a method for preventing or treating a condition, disorder or disease associated with a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition as described herein. In some embodiments, the base sequence of the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of the target nucleic acid comprising a target adenosine. In some embodiments, cells, tissues or organs associated with the condition, disorder or disease comprise or express an ADAR protein. In some embodiments, cells, tissues or organs associated with the condition, disorder or disease comprise or express ADAR1 (e.g., a p110 and/or a p150 forms). In some embodiments, cells, tissues or organs associated with the condition, disorder or disease comprise or express ADAR2. In some embodiments, a condition, disorder or disease is as described herein. In some embodiments, a condition, disorder or disease is alpha-1 antitrypsin deficiency. In some embodiments, a method comprises converting a target adenosine to I.

[001066] In some embodiments, the present disclosure provides an oligonucleotide comprising a sequence complementary to a target sequence. In some embodiments, the present disclosure provides an oligonucleotide which directs site-specific (can also be referred as site directed) editing (e.g., deamination). In some embodiments, the present disclosure provides an oligonucleotide which directs site-specific adenosine editing mediated by ADAR (e.g., an endogenous ADAR). Various provided oligonucleotides can be utilized as single-stranded oligonucleotides for site-directed editing of a nucleotide in a target RNA sequence. In some

embodiments, the present disclosure provides methods for preventing and/or treating conditions, disorders, or diseases associated with a G to A mutation in a target sequence using provided single-stranded oligonucleotides for site-directed editing of a nucleotide in a target RNA sequence and compositions thereof. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for use as medicaments, e.g., for conditions, disorders, or diseases associated with a G to A mutation in a target sequence. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for use in the treatment of conditions, disorders or diseases associated with a G to A mutation in a target sequence. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for the manufacture of medicaments for the treatment of a related conditions, disorders or diseases associated with a G to A mutation in a target sequence.

[001067] In some embodiments, the present disclosure provides a method for preventing, treating or ameliorating a condition, disorder or disease associated with a G to A mutation in a target sequence in a subject susceptible thereto or suffering therefrom, comprising administering to the subject a therapeutically effective amount of an oligonucleotide or a pharmaceutical composition thereof.

[001068] In some embodiments, the present disclosure provides a method for deaminating a target adenosine in a target sequence in a cell, comprising: contacting the cell with an oligonucleotide or a composition thereof. In some embodiments, the present disclosure provides a method deaminating a target adenosine in a target sequence (e.g., a transcript) in a cell, comprising: contacting the cell with an oligonucleotide or a composition thereof. In some embodiments, the present disclosure provides a method for reducing the level of a protein associated with a G to A mutation in a cell, comprising: contacting the cell with an oligonucleotide or a composition thereof. In some embodiments, provided methods can selectively reduce levels of a transcripts and/or products encoded thereby that are related to conditions, disorders or diseases associated with a G to A mutation. In some embodiments, provided methods can selectively edit target nucleic acids, e.g., transcripts comprising an undesired A (e.g., a G to A mutation) over otherwise identical nucleic acids which have G at positions of target A.

[001069] In some embodiments, the present disclosure provides a method for decreasing a mutated gene (e.g., a G to A mutation) expression in a mammal in need thereof, comprising administering to the mammal a nucleic acid-lipid particle comprising a provided single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence or a composition thereof.

[001070] In some embodiments, the present disclosure provides a method for in vivo delivery of an oligonucleotide, comprising administering to a mammal an oligonucleotide or a composition thereof.

[001071] In some embodiments, a subject or patient suitable for treatment of a condition, disorder, or disease associated with a G to A mutation, can be identified or diagnosed by a health care professional.

[001072] In some embodiments, a symptom of a condition, disorder or disease associated with a G to A mutation can be any condition, disorder or disease that can benefit from an A to I conversion.

[001073] In some embodiments, a provided single-stranded oligonucleotide for site-directed editing of a

nucleotide in a target RNA sequence or a composition thereof can prevent, treat, ameliorate, or slow progression of a condition, disorder or disease associated with a G to A mutation, or at least one symptom of a condition, disorder or disease associated with a G to A mutation.

[001074] In some embodiments, a method of the present disclosure can be for the treatment of a condition, disorder or disease associated with a G to A mutation in a subject wherein the method comprises administering to a subject a therapeutically effective amount of an oligonucleotide or a pharmaceutical composition thereof.

[001075] In some embodiments, a provided method can reduce at least one symptom of a condition, disorder or disease associated with a G to A mutation wherein the method comprises administering to a subject a therapeutically effective amount of an oligonucleotide or a pharmaceutical composition thereof.

[001076] In some embodiments, administration of an oligonucleotide to a patient or subject can be capable of mediating any one or more of: slowing the progression of a condition, disorder or disease associated with a G to A mutation; delaying the onset of a condition, disorder or disease associated with a G to A mutation or at least one symptom thereof; improving one or more indicators of a condition, disorder or disease associated with a G to A mutation; and/or increasing the survival time or lifespan of the patient or subject.

[001077] In some embodiments, slowing disease progression can relate to the prevention of, or delay in, a clinically undesirable change in one or more clinical parameters in an individual susceptible to or suffering from a condition, disorder, or disease associated with a G to A mutation, such as those described herein. It is well within the abilities of a physician to identify a slowing of disease progression in an individual susceptible to or suffering a condition, disorder, or disease associated with a G to A mutation, using one or more of the disease assessment tests described herein. Additionally, it is understood that a physician may administer to the individual diagnostic tests other than those described herein to assess the rate of disease progression in an individual susceptible to or suffering from a condition, disorder, or disease associated with a G to A mutation.

[001078] A physician may use family history of a condition, disorder, or disease associated with a G to A mutation or comparisons to other patients with similar genetic profile.

[001079] In some embodiments, indicators of a condition, disorder, or disease associated with a G to A mutation include parameters employed by a medical professional, such as a physician, to diagnose or measure the progression of the condition, disorder, or disease.

[001080] In some embodiments, a subject is administered an oligonucleotide or a composition thereof and an additional agent and/or method, e.g., an additional therapeutic agent and/or method. In some embodiments, an oligonucleotide or composition thereof can be administered alone or in combination with one or more additional therapeutic agents and/or treatment. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. In some embodiments, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. In some embodiments, provided oligonucleotides and additional therapeutic components are administered concurrently. In some embodiments, provided oligonucleotides and additional therapeutic components can be administered as one composition. In some embodiments, at a time point a subject being

administered can be exposed to both provided oligonucleotides and additional components at the same time.

[001081] In some embodiments, an additional therapeutic agent can be physically conjugated to an oligonucleotide. In some embodiments, an additional agent is GalNAc. In some embodiments, a provided single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence can be physically conjugated with an additional agent. In some embodiments, additional agent oligonucleotides can have base sequences, sugars, nucleobases, internucleotidic linkages, patterns of sugar, nucleobase, and/or internucleotidic linkage modifications, patterns of backbone chiral centers, etc., or any combinations thereof, as described in the present disclosure, wherein each T may be independently replaced with U and vice versa. In some embodiments, an oligonucleotide can be physically conjugated to a second oligonucleotide which can decrease (directly or indirectly) the expression, activity, and/or level of a target sequence , or which is useful for treating a condition, disorder, or disease associated with a G to A mutation.

[001082] In some embodiments, a provided single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence may be administered with one or more additional (or second) therapeutic agent for a condition, disorder or disease associated with a G to A mutation.

[001083] In some embodiments, a subject can be administered an oligonucleotide and an additional therapeutic agent, wherein the additional therapeutic agent is an agent described herein or known in the art which is useful for treatment of a condition, disorder or disease to be treated.

[001084] In some embodiments, provided single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence can be co-administered or be used as part of a treatment regimen along with one or more treatment for a condition, disorder or disease or a symptom thereof, including but not limited to: aptamers, lncRNAs, lncRNA inhibitors, antibodies, peptides, small molecules, other oligonucleotides to a target other targets.

[001085] In some embodiments, an additional therapeutic treatment is, as a non-limiting example, a method of editing a gene

[001086] In some embodiments, an additional therapeutic agent is, as a non-limiting example, an oligonucleotide.

[001087] In some embodiments, a second or additional therapeutic agent can be administered to a subject prior, simultaneously with, or after an oligonucleotide. In some embodiments, a second or additional therapeutic agent can be administered multiple times to a subject, and an oligonucleotide is also administered multiple times to a subject, and the administrations are in any order.

[001088] In some embodiments, an improvement may include decreasing the expression, activity and/or level of a gene or gene product which is too high in a disease state; increasing the expression, activity and/or level of a gene or gene product which is too low in the disease state; and/or decreasing the expression, activity and/or level of a mutant and/or disease-associated variant of a gene or gene product.

[001089] In some embodiments, an oligonucleotide or composition useful for treating, ameliorating and/or preventing a condition, disorder or disease associated with a G to A mutation can be administered (e.g., to a

subject) via various suitable available technologies.

[001090] In some embodiments, provided oligonucleotides, e.g., single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequences, can be administered as a pharmaceutical composition, e.g., for treating, ameliorating and/or preventing conditions, disorders or diseases. In some embodiments, provided oligonucleotides comprise at least one chirally controlled internucleotidic linkage. In some embodiments, provided oligonucleotide compositions are chirally controlled.

[001091] Among other things, technologies, e.g., oligonucleotides and compositions thereof, of the present disclosure can provide various improvements and advantages compared to reference technologies (e.g., absence or low levels of chiral control (e.g., stereorandom oligonucleotide compositions (e.g., of oligonucleotides of the same base sequence, or the same constitution, etc.)), and/or absence or low levels of certain modifications and patterns thereof (e.g., 2'-F, non-negatively charged internucleotidic linkages , etc.), such as improved stability, delivery, editing efficiency, pharmacokinetics, and/or pharmacodynamics. In some embodiments, a reference oligonucleotide composition is a stereorandom oligonucleotide composition of oligonucleotides with the same base sequence. In some embodiments, a reference oligonucleotide composition is a stereorandom oligonucleotide composition of oligonucleotides with the same constitution (as appreciated by those skilled in the art, in some embodiments, various salt forms may be properly considered to be of the same constitution). In some embodiments, a reference oligonucleotide is an oligonucleotide comprising no non-negatively charged internucleotidic linkages. In some embodiments, a reference oligonucleotide comprises no n001. In some embodiments, a reference oligonucleotide composition is a composition of oligonucleotides comprising no non-negatively charged internucleotidic linkages. In some embodiments, a reference oligonucleotide composition is a composition of oligonucleotides comprising no n001. In some embodiments, provided technologies may be utilized at lower unit or total doses, and/or may be administered with fewer doses and/or longer dose intervals (e.g., to achieve comparable or better effects) compared to reference technologies. In some embodiments, provided technologies can provide long durability of editing. In some embodiments, provided technologies once administered can provide activities, e.g., target editing, at or above certain levels (e.g., levels useful and/or sufficient to provide certain biological and/or therapeutic effects) for a period of time, e.g., about or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60 or more days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 months, after a last dose. In some embodiments, provided technologies provide low toxicity. In some embodiments, provided technologies may be utilized at higher unit or total doses, and/or may be administered with more doses and/or shorter dose intervals (e.g., to achieve better effects) compared to reference technologies. In some embodiments, a total dose may be administered as a single dose. In some embodiments, a total dose may be administered as two or more single doses. In some embodiments, a total dose administered as a single dose may provide higher maximum editing levels compared to when administered as two or more single doses.

[001092] In some cases, patients who have been administered an oligonucleotide as a medicament may experience certain side effects or adverse effects, including: thrombocytopenia, renal toxicity,

glomerulonephritis, and/or coagulation abnormalities; genotoxicity, repeat-dose toxicity of target organs and pathologic effects; dose response and exposure relationships; chronic toxicity; juvenile toxicity; reproductive and developmental toxicity; cardiovascular safety; injection site reactions; cytokine response complement effects; immunogenicity; and/or carcinogenicity. In some embodiments, an additional therapeutic agent is administered to counter-act a side effect or adverse effect of administration of an oligonucleotide. In some embodiments, a particular single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence can have a reduced capability of eliciting a side effect or adverse effect, compared to a different single-stranded oligonucleotide for site-directed editing of a nucleotide in a target RNA sequence.

[001093] In some embodiments, an additional therapeutic agent can be administered to the patient in order to control or alleviate one or more side effects or adverse effects associated with administration of an oligonucleotide.

[001094] In some embodiments, an oligonucleotide and one or more additional therapeutic agent can be administered to a patient (in any order), wherein the additional therapeutic agent can be administered to the patient in order to control or alleviate one or more side effects or adverse effects associated with administration of the oligonucleotide.

[001095] In some embodiments, an oligonucleotide and one or more additional therapeutic agent can be administered to a patient (in any order), wherein the additional therapeutic agent can be administered to the patient in order to control or alleviate one or more side effects or adverse effects associated with administration of the oligonucleotide.

[001096] In some embodiments, an oligonucleotide and one or more additional therapeutic agent can be administered to a patient (in any order), wherein the additional therapeutic agent can be administered to the patient in order to control or alleviate one or more side effects or adverse effects associated with administration of the oligonucleotide, and wherein the oligonucleotide operates via any biochemical mechanism, including but not limited to: decreasing the level, expression and/or activity of a target gene or a gene product thereof, increasing or decreasing skipping of one or more exons in a target gene mRNA, an ADAR-mediated deamination, a RNaseH-mediated mechanism, a steric hindrance-mediated mechanism, and/or a RNA interference-mediated mechanism, wherein the oligonucleotide is single- or double-stranded.

[001097] In some embodiments, an oligonucleotide composition and one or more additional therapeutic agent can be administered to a patient (in any order), wherein the additional therapeutic agent can be administered to the patient in order to control or alleviate one or more side effects or adverse effects associated with administration of the oligonucleotide composition, and wherein the oligonucleotide composition can be chirally controlled or comprises at least one chirally controlled internucleotidic linkage (including but not limited to a chirally controlled phosphorothioate).

[001098] Various conditions, disorders, or diseases can benefit from adenosine editing, including those are associated with a G to A mutation, e.g., Cystic fibrosis, Hurler Syndrome, alpha-1 -antitrypsin (A1AT) deficiency, Parkinson's disease, Alzheimer's disease, albinism, Amyotrophic lateral sclerosis, Asthma, β-

thalassemia, Cadasil syndrome, Charcot-Marie-Tooth disease, Chronic Obstructive Pulmonary Disease (COPD), Distal Spinal Muscular Atrophy (DSMA), Duchenne/Becker muscular dystrophy, Dystrophic Epidermolysis bullosa, Epidermylosis bullosa, Fabry disease, Factor V Leiden associated disorders, Familial Adenomatous, Polyposis, Galactosemia, Gaucher's Disease, Glucose-6-phosphate dehydrogenase, Haemophilia, Hereditary Hematochromatosis, Hunter Syndrome, Huntington's disease, Inflammatory Bowel Disease (IBD), Inherited polyagglutination syndrome, Leber congenital amaurosis, Lesch-Nyhan syndrome, Lynch syndrome, Marfan syndrome, Mucopolysaccharidosis, Muscular Dystrophy, Myotonic dystrophy types I and II, neurofibromatosis, Niemann-Pick disease type A, B and C, NY-eso1 related cancer, Peutz-Jeghers Syndrome, Phenylketonuria, Pompe's disease, Primary Ciliary Disease, Prothrombin mutation related disorders, such as the Prothrombin G20210A mutation, Pulmonary Hypertension, Retinitis Pigmentosa, Sandhoff Disease, Severe Combined Immune Deficiency Syndrome (SCID), Sickle Cell Anemia, Spinal Muscular Atrophy, Stargardt's Disease, Tay-Sachs Disease, Usher syndrome, X-linked immunodeficiency, Sturge-Weber Syndrome, and various cancers. Certain conditions, disorders or diseases are described in WO 2020/154344, WO 2020/154343, WO 2020/154342, WO 2020/165077, WO 2020/201406, WO 2020/216637, or WO 2020/252376.

[001099] In some embodiments, a condition, disorder or disease is Alpha-1 antitrypsin (A1AT) deficiency (AATD).

[001100] Alpha-1 antitrypsin (A1AT) deficiency (AATD) is a genetic disease reportedly caused by defects in the SERPINA1 gene (also known as PI; AIA; AAT; PIl; A1AT; PR02275; and alpha1AT). Severe A1AT deficiency is associated with various phenotypes including lung and liver phenotypes.

[001101] A1AT deficiency is reportedly one of the most common genetic diseases in subjects of Northern European descent. Prevalence of severe A1AT deficiency in the U.S. alone is 80,000-100,000. Similar numbers are estimated to be found in the EU. The worldwide estimate for severe A1AT deficiency has been pegged at 3 million people. A1AT deficiency causes emphysema, with subjects developing emphysema in their third or fourth decade. A1AT deficiency can also cause liver failure and hepatocellular carcinoma, with up to 30% of subjects with severe A1AT deficiency developing significant liver disease, including cirrhosis, fulminant liver failure, and hepatocellular carcinoma.

[001102] A mutation (i.e., c. 1024G>A) in SERPINA1 gene leads to a glutamate to lysine substitution at amino acid position 342 (E342K, "Z mutation") of the mature A1AT protein. This missense mutation affect protein conformation and secretion leading to reduced circulating levels of A1AT. Alleles carrying the Z mutation are identified as PiZ alleles. Subjects homozygous for the PiZ allele are termed PiZZ carriers, and express 10-15% of normal levels of serum A1AT. Approximately 95% of subjects who are symptomatic for A1AT deficiency have the PiZZ genotype. Subjects heterozygous for the Z mutation are termed PiMZ mutants, and express 60% of normal levels of serum A1AT. Of those diagnosed, 90% of patients with severe A1AT deficiency have the ZZ mutation. About between 30,000 and 50,000 individuals in the United States have the PiZZ genotype.

[001103] The pathophysiology of A1AT deficiency can vary by the organ affected. Liver disease is reported to be due to a gain-of-function mechanism. Abnormally folded A1AT, especially Z-type A1AT (Z-AT), aggregates and polymerizes within hepatocytes. A1AT inclusions are found in PiZZ subjects and are thought to cause cirrhosis and, in some cases, hepatocellular carcinoma. Evidence for the gain-of-function mechanism in liver disease is supported by null homozygotes. These subjects produce no A1AT and do not develop hepatocyte inclusions or liver disease.

[001104] It is reported that A1AT deficiency leads to liver disease in up to about 50% of A1AT subjects and leads to severe liver disease in up to about 30% of subjects. Liver disease may manifest as: (a) cirrhosis during childhood that is self-limiting, (b) severe cirrhosis during childhood or adulthood that requires liver transplantation or leads to death and (c) hepatocellular carcinoma that is often deadly. The onset of liver disease is reported to be bi-modal, predominantly affecting children or adults. Childhood disease is self-limiting in many cases but may be led to end-stage, deadly cirrhosis. It is reported that up to about 18% of subjects with the PiZZ genotype may develop clinically significant liver abnormalities during childhood. Approximately 2% of PiZZ subjects are reported to develop severe liver cirrhosis leading to death during childhood (Sveger 1988; Volpert 2000). Adult-onset liver disease may affect subjects with all genotypes, but presents earlier in subjects with the PiZZ genotype . Approximately 2-10% of A1AT deficient subjects are reported to develop adult-onset liver disease.

[001105] Lung disease associated with A1AT deficiency is currently treated with intravenous administration of human-derived replacement A1AT protein, but in addition to being costly and requiring frequent injections over a subject's entire lifetime, this approach is only partially effective. AlAT-deficient subjects with hepatocellular carcinoma are currently treated with chemotherapy and surgery, but there is no satisfactory approach for preventing the potentially deadly liver manifestations of A1AT deficiency.

[001106] Among other things, the present disclosure recognizes a need for improved treatment of A1AT deficiency, e.g., including liver and lung manifestations thereof. In some embodiments, the present disclosure provides technologies for preventing or treating conditions, disorders or diseases associated Alpha-1 antitrypsin (A1AT) deficiency, e.g., by providing oligonucleotides and/or compositions that can convert the A mutation to I which can be read as G during protein translation and thus correcting the G to A mutation for protein translation. Among other things, alteration of SERPINA1 in one or more of hepatocytes can prevent the progression of liver disease in subjects with A1AT deficiency by reducing or eliminating production of the toxic Z protein (Z-AAT). In certain embodiments, Z protein production is eliminated or reduced by utilizing provided technologies. In certain embodiments, the disease is cured, does not progress, or has delayed progression compared to a subject who has not received the therapy.

[001107] In some embodiments, AATD dual pathologies have been reported in liver and lung. In some embodiments, inability to secrete polymerized Z-ATT has been reported to lead to, e.g., liver damage/cirrhosis. In some embodiments, one or both lungs are open to unchecked proteases, which in some embodiments lead to inflammation and lung damage. Many patients (e.g., reportedly ~200,000 in the US and EU) are with

homozygous ZZ genotype which is reported to be associated with the most common form of sever AATD. It has been reported that approved therapies modestly increase circulating levels of wide-type AAT in those with lung pathology, and no therapies address liver pathology. In some embodiments, provided technologies increase or restore expression, levels, properties and/or activities of wild-type AAT in liver. In some embodiments, provided technologies target liver, e.g., through incorporating moieties targeting liver (e.g., ligands such as GalNAc targeting receptors expressed in liver) into oligonucleotides. In some embodiments, provided technologies restore, increase or enhance wild-type AAT physiological regulation in liver. In some embodiments, provided technologies reduce Z-AAT protein aggregation. In some embodiments, provided technologies restore, increase or enhance wild-type AAT physiological regulation in liver and reduce Z-AAT protein aggregation. In some embodiments, provided technologies increase secretion into bloodstream. In some embodiments, provided technologies increase circulating wild-type AAT. In some embodiments, provided technologies increase circulating, lung-bond wild-type AAT. In some embodiments, provided technologies increase or restore expression, levels, properties and/or activities of wild-type AAT in lung. In some embodiments, provided technologies protect lungs from undesired proteases. In some embodiments, provided technologies reduce or prevent inflammation and/or lung damage. In some embodiments, provided technologies provide benefits at both livers and lungs. In some embodiments, provided technology reduces or prevents liver damage or cirrhosis, and reduces or prevents inflammation and/or lung damage. In some embodiments, provided oligonucleotides, e.g., those comprising certain moieties such ligands (e.g., GalNAc) targeting receptors expressed in livers, provide benefits at livers and lungs. In some embodiments, provided technologies simultaneously provide benefits at livers and lungs. In some embodiments, provided technologies address lung and/or liver manifestation of AATD. In some embodiments, provided technologies simultaneously address lung and liver manifestation of AATD. In some embodiments, provided technologies comprise using GalNAc conjugated oligonucleotides and compositions thereof to correct RNA base mutation in mRNA coded by SERPINA1 Z allele that triggers AATD. In some embodiments, provided technologies simultaneously reduce aggregation of mutated, misfolded alpha-1 protein and increase circulating levels of wild-type alpha-1 antitrypsin protein, and in some embodiments address both liver and lung manifestations of AATD. In some embodiments, provided technologies avoid risk of permanent off-target changes to DNA.

[001108] In certain embodiments, technologies as described herein can provide a selective advantage to survival of one or more of treated hepatocytes. In certain embodiments, a target cell is modified. In some embodiments, cells treated with technologies herein may not produce toxic Z protein. In some embodiments, diseased cells that are not modified produce toxic Z proteins and may undergo apoptosis secondary to endoplasmic reticulum (ER) stress induced by Z protein misfolding. In certain embodiments, after treatment using the provided technologies, treated cells will survive and untreated cells will die. This selective advantage can drive eventual colonization of hepatocytes with the majority being SERPINA1 corrected cells.

[001109] In some embodiments, an oligonucleotide, when administered to a patient suffering from or susceptible to a condition, disorder or disease that is associated with a G to A mutation is capable of reducing

at least one symptom of the condition, disorder or disease and/or capable of delaying or preventing the onset, worsening, and/or reducing the rate and/or degree of worsening of at least one symptom of the condition, disorder or disease that's due to a G to A mutation in a gene or gene product.

[001110] In some embodiments, provided technologies can provide editing of two or more sites in a system (e.g., a cell, tissue, organ, animal, etc.) ("multiplex editing"). In some embodiments, provided technologies can target and provide editing of two or more sites of the same transcripts. In some embodiments, provided technologies can target and provide editing of two or more different transcripts, either from the same nucleic acid or different nucleic acids. In some embodiments, provided technologies can target and provide editing of transcripts from two or more different nucleic acids. In some embodiments, provided technologies can target and provide editing of transcripts from two or more different genes. In some embodiments, of the targets simultaneously edited, each is independently at a biologically and/or therapeutically relevant level. In some embodiments, in multiplex editing one or more or all targets are independently edited at a comparable level as editing conducted individually under comparable conditions. In some embodiments, multiplex editing are performed utilizing two or more separate compositions, each of which independently target one or more targets. In some embodiments, compositions are administered concurrently. In some embodiments, compositions are administered with suitable intervals. In some embodiments, one or more compositions are administered prior or subsequently to one or more other compositions. In some embodiments, multiplex editing are performed utilizing a single composition, e.g., a composition comprising two or more pluralities of oligonucleotides, wherein the pluralities target different targets. In some embodiments, each plurality independently targets a different adenosine. In some embodiments, each plurality independently targets a different transcript. In some embodiments, each plurality independently targets a different gene. In some embodiments, two or more pluralities may target the same target, but the pluralities together target the desired targets.

[001111] As described herein, provided technologies can provide a number of advantages. For example, in some embodiments, provided technologies are safer than technologies that act on DNA, as provided technologies can provide RNA edits that are both reversible and tunable (e.g., through adjusting of doses). Additionally and alternatively, as demonstrated herein, provided technologies can provide high levels of editing in systems expressing endogenous ADAR proteins thus avoiding the requirement of introduction of exogenous proteins in various instances. Still further, provided technologies do not require complex oligonucleotides that depend on ancillary delivery vehicles, such as viral vectors or lipid nanoparticles, as utilized in many other technologies, particularly for application beyond cell culture. In some embodiments, provided technologies can provide sequence-specific A-to-I RNA editing with high efficiency using endogenous ADAR enzymes and can be delivered to various systems, e.g., cells, in the absence of artificial delivery agents.

[001112] Those skilled in the art reading the present disclosure will understand that provided oligonucleotides and compositions thereof may be delivered using a number of technologies in accordance with the present disclosure. In some embodiments, provided oligonucleotides and compositions may be

delivered via transfection or lipofeciton. In some embodiments, provided oligonucleotides and compositions thereof may be delivered in the absence of delivery aids, such as those utilized in transfection or lipofection. In some embodiments, provided oligonucleotides and compositions may be delivered via transfection or lipofeciton. In some embodiments, provided oligonucleotides and compositions thereof are delivered with gymnotic delivery. In some embodiments, provided oligonucleotides comprise additional chemical moieties that can facilitate delivery. For example, in some embodiments, additional chemical moieties are or comprise ligand moieties (e.g., *N*-acetylgalactosamine (GalNAc)) for receptors (e.g., asialoglycoprotein receptors). In some embodiments, provided oligonucleotides and compositions thereof can be delivered through GalNAc-mediated delivery.

[001113] Among other things, the present disclosure provides the following Example Embodiments:

1. An oligonucleotide comprising:

a first domain; and

a second domain,

wherein:

the first domain comprises one or more 2'-F modifications;

the second domain comprises one or more sugars that do not have a 2'-F modification.

2. An oligonucleotide comprising a modified nucleobase, nucleoside, sugar or internucleotidic linkage as described in the present disclosure.

3. An oligonucleotide, wherein about or at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of all sugars are 2'-F modified sugars.

4. An oligonucleotide comprising a second subdomain as described in the present disclosure.

5. An oligonucleotide comprising one or more modified sugars and/or one or more modified internucleotidic linkages, wherein the oligonucleotide comprises a first domain and a second domain each independently comprising one or more nucleobases.

6. The oligonucleotide of any one of Embodiments 1-5, wherein when the oligonucleotide is contacted with a target nucleic acid comprising a target adenosine in a system, a target adenosine in the target nucleic acid is modified.

7. The oligonucleotide of any one of Embodiments 1-5, wherein when the oligonucleotide is contacted with a target nucleic acid comprising a target adenosine in a system, level of the target nucleic acid is reduced compared to absence of the product or presence of a reference oligonucleotide.

8. The oligonucleotide of any one of Embodiments 1-5, wherein when the oligonucleotide is contacted with a target nucleic acid comprising a target adenosine in a system, splicing of the target nucleic acid or a product thereof is altered compared to absence of the oligonucleotide or presence of a reference oligonucleotide.

9. The oligonucleotide of any one of Embodiments 1-5, wherein when the oligonucleotide is contacted with a target nucleic acid comprising a target adenosine in a system, level of a product of the target nucleic

acid is altered compared to absence of the product or presence of a reference oligonucleotide.

10. The oligonucleotide of any one of Embodiments 7-9, wherein the target nucleic acid is modified.

11. The oligonucleotide of any one of Embodiments 6-10, wherein level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to the target nucleic acid but the target adenosine is modified.

12. The oligonucleotide of any one of Embodiments 6-10, wherein level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to the target nucleic acid but the target adenosine is replaced with inosine.

13. The oligonucleotide of any one of Embodiments 6-10, wherein level of a product is increased, wherein the product is or is encoded by a nucleic acid which is otherwise identical to the target nucleic acid but the adenine of the target adenosine is replaced with guanine.

14. The oligonucleotide of any one of Embodiments 11-13, wherein the product is a protein.

15. The oligonucleotide of any one of the preceding Embodiments, wherein the target adenosine is a mutation from guanine.

16. The oligonucleotide of any one of the preceding Embodiments, wherein the target adenosine is more associated with a condition, disorder or disease than a guanine at the same position.

17. The oligonucleotide of any one of the preceding Embodiments, wherein the target adenosine is associated with alpha-1 antitrypsin (A1AT) deficiency.

18. The oligonucleotide of any one of the preceding Embodiments, wherein the target adenosine is in human SERPINA1 gene.

19. The oligonucleotide of any one of the preceding Embodiments, wherein the target adenosine is 1024 G>A (E342K) mutation in human SERPINA1 gene.

20. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is capable of forming a double-stranded complex with the target nucleic acid.

21. The oligonucleotide of Embodiment 6-20, wherein a target nucleic acid or a portion thereof is or comprises RNA.

22. The oligonucleotide of any one of Embodiments 6-21, wherein the target adenosine is of an RNA.

23. The oligonucleotide of any one of Embodiments 6-22, wherein the target adenosine is modified, and the modification is or comprises deamination of the target adenosine.

24. The oligonucleotide of any one of Embodiments 6-23, wherein the target adenosine is modified and the modification is or comprises conversion of the target adenosine to an inosine.

25. The oligonucleotide of any one of Embodiments 6-24, wherein the modification is promoted by an ADAR protein.

26. The oligonucleotide of any one of Embodiments 6-25, wherein the system is an *in vitro* or *ex vivo* system comprising an ADAR protein.

27. The oligonucleotide of any one of Embodiments 6-25, wherein the system is or comprises a cell that

comprises or expresses an ADAR protein.

28. The oligonucleotide of any one of Embodiments 6-25, wherein the system is a subject comprising a cell that comprises or expresses an ADAR protein.

29. The oligonucleotide of any one of Embodiments 25-28, wherein the ADAR protein is ADAR1.

30. The oligonucleotide of any one of Embodiments 25-28, wherein the ADAR protein is ADAR2.

31. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 10-200 (e.g., about 10-20, 10-30, 10-40, 10-50, 10-60, 10-70, 10-80, 10-90, 10-100, 10-120, 10-150, 20-30, 20-40, 20-50, 20-60, 20-70, 20-80, 20-90, 20-100, 20-120, 20-150, 20-200, 25-30, 25-40, 25-50, 25-60, 25-70, 25-80, 25-90, 25-100, 25-120, 25-150, 25-200, 30-40, 30-50, 30-60, 30-70, 30-80, 30-90, 30-100, 30-120, 30-150, 30-200, 10, 20, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 60, etc.) nucleobases.

32. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 26-35 nucleobases.

33. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 26 nucleobases.

34. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 27 nucleobases.

35. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 28 nucleobases.

36. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 29 nucleobases.

37. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 30 nucleobases.

38. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 31 nucleobases.

39. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 32 nucleobases.

40. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 33 nucleobases.

41. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 34 nucleobases.

42. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a length of about 35 nucleobases.

43. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is complementary to a base sequence of a portion of the target nucleic acid comprising the target adenosine with 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-

8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches which are not Watson-Crick base pairs.

44. The oligonucleotide of Embodiment 43, wherein one or more mismatches are independently a wobble base paring.

45. The oligonucleotide of any one of Embodiments 43-44, wherein the complementarity is about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.).

46. The oligonucleotide of any one of Embodiments 43-44, wherein the complementarity is about 90%-100% or about 95-100%.

47. The oligonucleotide of any one of Embodiments 43-44, wherein the complementarity is 100%.

48. The oligonucleotide of any one of Embodiments 43-44, wherein the complementarity is 100% except at a nucleoside opposite to a target nucleoside (e.g., adenosine).

49. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide consists of a first domain and a second domain.

50. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain has a length of about 2-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases.

51. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain has a length of about 10-25 nucleobases.

52. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain has a length of about 15 nucleobases.

53. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

54. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises two or more mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

55. The oligonucleotide of any one of Embodiments 1-50, wherein the first domain comprises one and no more than one mismatch when the oligonucleotide is aligned with a target nucleic acid for complementarity.

56. The oligonucleotide of any one of Embodiments 1-50, wherein the first domain comprises two and no more than two mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

57. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges when the oligonucleotide is aligned with a target nucleic acid for complementarity.

58. The oligonucleotide of Embodiment 57, wherein each bulge independently comprises one or more base pairs that are not Watson-Crick or wobble pairs.

59. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

60. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises two or more wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

61. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises two and no more than two wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

62. The oligonucleotide of any one of Embodiments 1-50, wherein the first domain is fully complementary to a target nucleic acid.

63. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) sugars with 2'-F modification.

64. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the first domain independently comprise a 2'-F modification.

65. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the first domain independently comprise a 2'-F modification.

66. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain independently comprise a 2'-F modification.

67. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in the first domain comprises 2'-OMe.

68. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain comprises 2'-OMe.

69. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 50% of sugars in the first domain comprises 2'-OMe.

70. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in the first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic.

71. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic.

72. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 50% of sugars in the first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic.

73. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 1%-95% (e.g., no more than about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, etc.) of sugars in the first domain comprises 2'-OR.

74. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain comprises 2'-OR, wherein R is not −H.

75. The oligonucleotide of any one of the preceding Embodiments, wherein no more than about 50% of sugars in the first domain comprises 2'-OR.

76. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic.

77. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-MOE modification.

78. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OMe modification.

79. The oligonucleotide of any one of the preceding Embodiments, wherein the first about 1-5, e.g., 1, 2, 3, 4, or 5 sugars from the 5'-end of a first domain is independently a 2'-OR modified sugar, wherein R is

independently optionally substituted C_{1-6} aliphatic.

80. The oligonucleotide of any one of the preceding Embodiments, wherein the first about 1-5, e.g., 1, 2, 3, 4, or 5 sugars from the 5'-end of a first domain is independently a 2'-MOE modified sugar.

81. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification, wherein each R is optionally substituted C_{1-6} aliphatic.

82. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification.

83. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) LNA sugars.

84. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

85. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-F modification.

86. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising 2'-OH.

87. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising two 2'-H.

88. The oligonucleotide of any one of Embodiments 1-75, wherein no sugar in the first domain comprises 2'-OR.

89. The oligonucleotide of any one of Embodiments 1-75, wherein no sugar in the first domain comprises 2'-OMe.

90. The oligonucleotide of any one of Embodiments 1-75, wherein no sugar in the first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic.

91. The oligonucleotide of any one of Embodiments 1-75, wherein each sugar in the first domain comprises 2'-F.

92. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic

linkages.

93. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the first domain are modified internucleotidic linkages.

94. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the first domain are modified internucleotidic linkages.

95. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a chiral internucleotidic linkage.

96. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

97. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage.

98. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more phosphorothioate internucleotidic linkages.

99. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises 1, 2, 3, 4, or 5 non-negatively charged internucleotidic linkages.

100. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the first domain is a non-negatively charged internucleotidic linkage.

101. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the first domain is a non-negatively charged internucleotidic linkage.

102. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the first domain is chirally controlled.

103. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the first domain is chirally controlled.

104. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the first domain is chirally controlled.

105. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the first domain is chirally controlled.

106. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

107. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the first domain is *S*p.

108. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the first domain is *S*p.

109. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkages in the first domain is *S*p.

110. The oligonucleotide of any one of Embodiments 1-108, wherein the internucleotidic linkage between the first and the second nucleosides of the first domain is *R*p.

111. The oligonucleotide of any one of Embodiments 1-108 and 110, wherein the internucleotidic linkage between the last and the second last nucleosides of the first domain is *R*p.

112. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage in the first domain is independently a modified internucleotidic linkage.

113. The oligonucleotide of any one of Embodiments 1-111, wherein the first domain comprises one or

more natural phosphate linkages.

114. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain can recruit, or promotes or contributes to recruitment of, an ADAR protein to a target nucleic acid.

115. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain can interact, or promotes or contributes to interaction of, an ADAR protein with a target nucleic acid.

116. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain contacts with a RNA binding domain (RBD) of ADAR.

117. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain does not substantially contact with a second RBD domain of ADAR.

118. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain does not substantially contact with a catalytic domain which has a deaminase activity, of ADAR.

119. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain has a length of about 2-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases.

120. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain has a length of about 1-7 nucleobases.

121. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain has a length of about 5-15 nucleobases.

122. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain has a length of about 10-25 nucleobases.

123. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain has a length of about 15 nucleobases.

124. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

125. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises two or more mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

126. The oligonucleotide of any one of Embodiments 1-119, wherein the second domain comprises one and no more than one mismatch when the oligonucleotide is aligned with a target nucleic acid for complementarity.

127. The oligonucleotide of any one of Embodiments 1-119, wherein the second domain comprises two and no more than two mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

128. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain

comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges when the oligonucleotide is aligned with a target nucleic acid for complementarity.

129. The oligonucleotide of Embodiment 128, wherein each bulge independently comprises one or more base pairs that are not Watson-Crick or wobble pairs.

130. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

131. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises two or more wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

132. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises two and no more than two wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

133. The oligonucleotide of any one of Embodiments 1-119, wherein the second domain is fully complementary to a target nucleic acid.

134. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprise a nucleoside opposite to a target adenosine when the oligonucleotide is aligned with a target nucleic acid for complementarity.

135. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is optionally substituted or protected U, or is an optionally substituted or protected tautomer of U.

136. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is U.

137. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is optionally substituted or protected C, or is an optionally substituted or protected tautomer of C.

138. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is C.

139. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is optionally substituted or protected A, or is an optionally substituted or protected tautomer of A.

140. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is A.

141. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is optionally substituted or protected nucleobase of pseudoisocytosine, or is an optionally substituted or protected tautomer of the nucleobase of pseudoisocytosine.

142. The oligonucleotide of Embodiment 134, wherein the opposite nucleobase is the nucleobase of pseudoisocytosine.

143. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises a nucleobase BA, wherein BA is or comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 hetereoatoms.

144. An oligonucleotide, wherein the oligonucleotide comprises a nucleobase BA, wherein BA is or

comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 hetereoatoms.

145. The oligonucleotide of Embodiment 134, wherein the nucleobase is BA, wherein BA is or comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 hetereoatoms.

146. The oligonucleotide of any one of Embodiments 143-145, wherein BA has weaker hydrogen bonding with the target adenine of the adenosine compared to U.

147. The oligonucleotide of any one of Embodiments 143-146, wherein BA forms fewer hydrogen bonds with the target adenine of the adenosine compared to U.

148. The oligonucleotide of any one of Embodiments 143-147, wherein BA forms one or more hydrogen bonds with one or more amino acid residues of ADAR which residues form one or more hydrogen bonds with U opposite to a target adenosine.

149. The oligonucleotide of any one of Embodiments 143-148, wherein BA forms one or more hydrogen bonds with each amino acid residue of ADAR that forms one or more hydrogen bonds with U opposite to a target adenosine.

150. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA comprises $=\!=\!=X^2=\!=\!=X^3=\!=\!=$.

151. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA comprises $=\!=\!=X^2=\!=\!=X^3=\!=\!=X^4=\!=\!=$.

152. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA comprises $-X^1(=\!=\!=)=\!=\!=X^2=\!=\!=X^3=\!=\!=$.

153. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA comprises $-X^1(=\!=\!=)=\!=\!=X^2=\!=\!=X^3=\!=\!=X^4=\!=\!=$.

154. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-I.

155. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-I-a.

156. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-I-b.

157. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-II.

158. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-II-a.

159. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-II-b.

160. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of

formula BA-III.

161. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-III-a.

162. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-III-b.

163. The oligonucleotide of any one of Embodiments 143-162, wherein each of X^1, X^2, X^3, X^4, X^5, X^6, $X^{1'}$, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−.

164. The oligonucleotide of any one of Embodiments 150-163, wherein X^1 is −N(−)−.

165. The oligonucleotide of any one of Embodiments 150-163, wherein X^1 is −C(−)=.

166. The oligonucleotide of any one of Embodiments 150-165, wherein X^2 is −C(O)−.

167. The oligonucleotide of any one of Embodiments 150-166, wherein X^3 is −NR'−.

168. The oligonucleotide of any one of Embodiments 150-167, wherein X^3 is optionally substituted −NH−.

169. The oligonucleotide of any one of Embodiments 150-167, wherein X^3 is −NH−.

170. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(R^{B4})=, −C(−N(R^{B4})$_2$)=, −C(R^{B4})$_2$−, or −C(=NR^{B4})−.

171. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(R^{B4})=.

172. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is optionally substituted −CH=.

173. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −CH=.

174. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(−N(R^{B4})$_2$)=.

175. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is optionally substituted −C(−NH_2)=.

176. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(−NH_2)=.

177. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(−N=CHNR_2)=.

178. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(−N=CHN(CH_3)$_2$)=.

179. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(−NHR')=.

180. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(R^{B4})$_2$−.

181. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is optionally substituted −CH_2−.

182. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −CH_2−.

183. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is optionally substituted −C(=NH)−.

184. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(=NR^{B4})−.

185. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(O)=, wherein the

oxygen atom has a weaker hydrogen bond acceptor than the corresponding −C(O)− in U.

186. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(O)=, wherein the oxygen atom forms an intramolecular hydrogen bond.

187. The oligonucleotide of any one of Embodiments 150-169, wherein X^4 is −C(O)=, wherein the oxygen atom forms an hydrogen bond with a hydrogen within the same nucleobase.

188. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-C(R^{B5})_2-$.

189. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is optionally substituted $-CH_2-$.

190. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-CH_2-$.

191. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-C(R^{B5})=$.

192. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is optionally substituted $-C(-NO_2)=$.

193. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is optionally substituted −CH=.

194. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is −CH=.

195. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-C(-L^{B5}-R^{B51})=$, wherein R^{B51} is −R', $-N(R')_2$, −OR', or −SR'.

196. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-C(-L^{B5}-R^{B51})=$, wherein R^{B51} is $-N(R')_2$, −OR', or −SR'.

197. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is $-C(-L^{B5}-R^{B51})=$, wherein R^{B51} is −NHR'.

198. The oligonucleotide of any one of Embodiments 195-197, wherein L^{B5} is or comprises −C(O).

199. The oligonucleotide of any one of Embodiments 157-187, wherein X^5 is −N=.

200. The oligonucleotide of any one of Embodiments 197-198, wherein X^4 is −C(O)=, wherein the oxygen atom forms a hydrogen bond with a hydrogen of −NHR', −OH or −SH in R^{B51}.

201. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-IV.

202. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-IV-a.

203. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-IV-b.

204. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-V.

205. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-V-a.

206. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of

formula BA-V-b.

207. The oligonucleotide of any one of Embodiments 143-153, wherein Ring BA has the structure of formula BA-VI.

208. The oligonucleotide of any one of Embodiments 201-207, wherein each of X^1, X^2, X^3, X^4, X^5, X^6, $X^{1'}$, $X^{2'}$, $X^{3'}$, $X^{4'}$, $X^{5'}$, $X^{6'}$, and $X^{7'}$ is independently and optionally substituted when it is −CH=, −C(OH)=, −C(−NH_2)=, −CH_2−, −C(=NH)−, or −NH−.

209. The oligonucleotide of any one of Embodiments 201-208, wherein X^1 is −N(−)−.

210. The oligonucleotide of any one of Embodiments 201-208, wherein X^1 is −C(−)=.

211. The oligonucleotide of any one of Embodiments 201-210, wherein X^2 is optionally substituted −CH=.

212. The oligonucleotide of any one of Embodiments 201-210, wherein X^2 is −CH=.

213. The oligonucleotide of any one of Embodiments 201-210, wherein X^2 is −C(O)−.

214. The oligonucleotide of any one of Embodiments 201-213, wherein X^3 is −NR'−.

215. The oligonucleotide of any one of Embodiments 201-213, wherein X^3 is optionally substituted −NH−.

216. The oligonucleotide of any one of Embodiments 201-213, wherein X^3 is −NH−.

217. The oligonucleotide of any one of Embodiments 201-216, wherein Ring BA^A is 5-membered.

218. The oligonucleotide of any one of Embodiments 201-216, wherein Ring BA^A is 6-membered.

219. The oligonucleotide of any one of Embodiments 201-218, wherein Ring BA^A is an optionally substituted ring having 1-3 heteroatoms.

220. The oligonucleotide of Embodiment 219, wherein a heteroatom is a nitrogen.

221. The oligonucleotide of any one of Embodiments 219 -220, wherein Ring BA^A contains two nitrogen.

222. The oligonucleotide of any one of Embodiments 219 -220, wherein a heteroatom is oxygen.

223. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is −C(R^{B6})=, −C(OR^{B6})=, −C(R^{B6})$_2$−, or −C(O)−.

224. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is −C(R)=, −C(R)$_2$−, or −C(O)−.

225. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is optionally substituted −CH=.

226. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is −CH=.

227. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is optionally substituted −CH_2−.

228. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is −CH_2−.

229. The oligonucleotide of any one of Embodiments 160-222, wherein X^6 is −C(O)−.

230. The oligonucleotide of any one of Embodiments 134-149, wherein Ring BA comprises $X^{4'}$ $X^{5'}$.

231. The oligonucleotide of any one of Embodiments 143-149 or 230, wherein Ring BA has the structure of formula BA-VI.

232. The oligonucleotide of Embodiment 230, wherein $X^{1'}$ is −N(−)−.

233. The oligonucleotide of Embodiment 230, wherein $X^{1'}$ is −C(−)=.

234. The oligonucleotide of any one of Embodiments 230-233, wherein $X^{2'}$ is −C(O)−.

235. The oligonucleotide of any one of Embodiments 230-233, wherein $X^{2'}$ is optionally substituted −CH=.

236. The oligonucleotide of any one of Embodiments 230-233, wherein $X^{2'}$ is −CH=.

237. The oligonucleotide of any one of Embodiments 230-233, wherein $X^{2'}$ is −C(−)=.

238. The oligonucleotide of any one of Embodiments 230-236, wherein $X^{3'}$ is −NR'−.

239. The oligonucleotide of any one of Embodiments 230-236, wherein $X^{3'}$ is optionally substituted −NH−.

240. The oligonucleotide of any one of Embodiments 230-236, wherein $X^{3'}$ is −NH−.

241. The oligonucleotide of any one of Embodiments 230-236, wherein $X^{3'}$ is −N=.

242. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is −C(O)=.

243. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is $-C(OR^{B4'})=$.

244. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is $-C(R^{B4'})=$.

245. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is optionally substituted −CH=.

246. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is −CH=.

247. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is $-C(-N(R^{B4'})_2)=$.

248. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is optionally substituted $-C(-NH_2)=$.

249. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is $-C(-NH_2)=$.

250. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is $-C(-N=CHN(CH_3)_2)=$.

251. The oligonucleotide of any one of Embodiments 230-241, wherein $X^{4'}$ is −C(−NC(O)R')=.

252. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is optionally substituted −NH−.

253. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is −NH−.

254. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is −N=.

255. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is $-C(R^{B5'})=$.

256. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is optionally substituted −CH=.

257. The oligonucleotide of any one of Embodiments 230-251, wherein $X^{5'}$ is −CH=.

258. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is $-C(R^{B6'})=$.

259. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is optionally substituted

−CH=.

260. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is −CH=.

261. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is −C(O)=.

262. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is $-C(OR^{B6'})=$.

263. The oligonucleotide of any one of Embodiments 230-257, wherein $X^{6'}$ is −C(OR')=.

264. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is $-C(R^{B7'})=$.

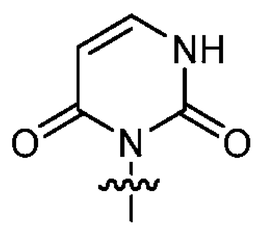
265. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is optionally substituted −CH=.

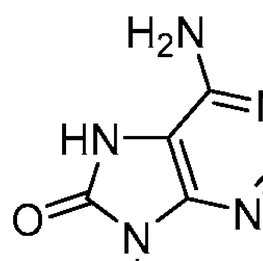
266. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is −CH=.

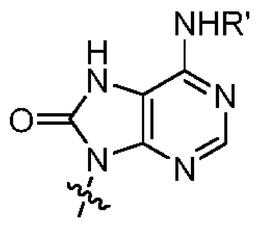
267. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is optionally substituted −NH−.

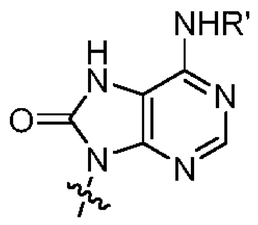
268. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is −NH−.

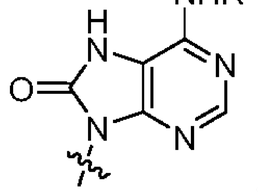
269. The oligonucleotide of any one of Embodiments 230-263, wherein $X^{7'}$ is −N=.

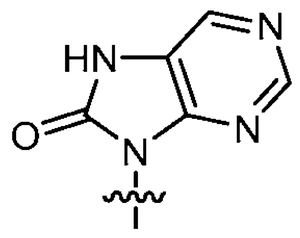
270. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

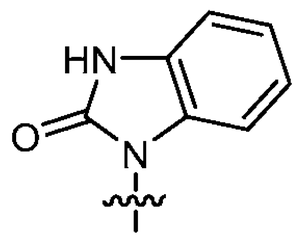
271. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

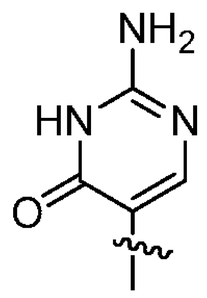
272. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

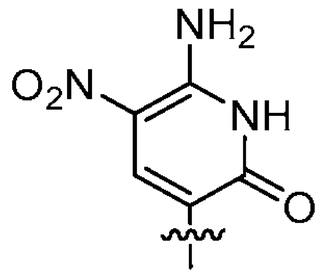
273. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  , wherein R' is −C(O)R.

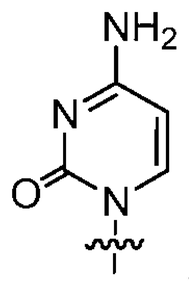
274. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  , wherein R' is −C(O)Ph.

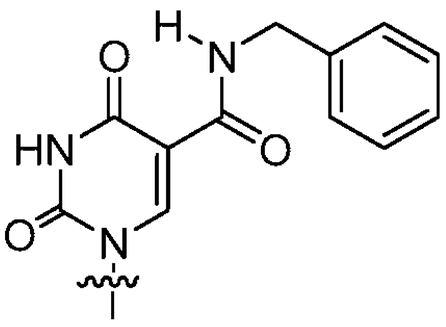
275. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

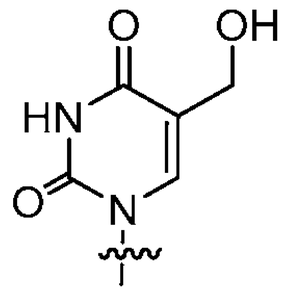
276. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

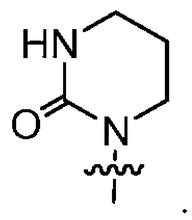
277. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

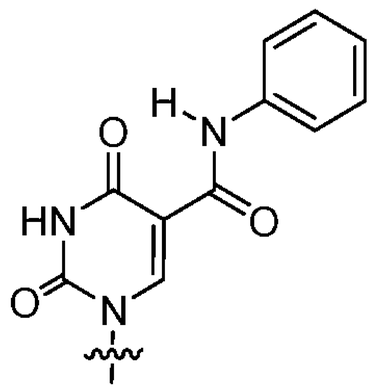
278. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

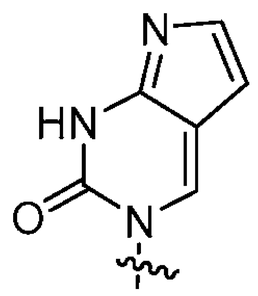
279. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

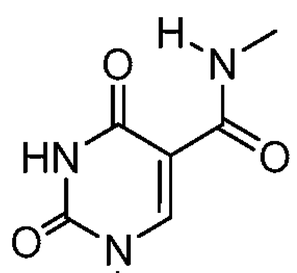
280. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

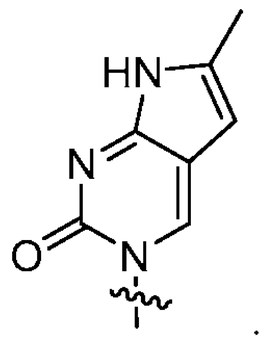
281. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

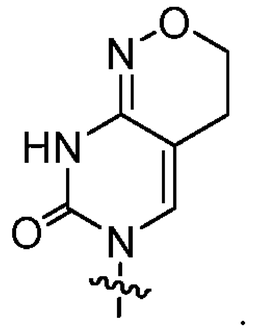
282. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

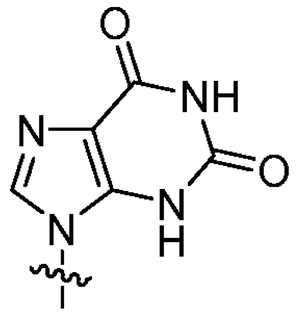
283. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

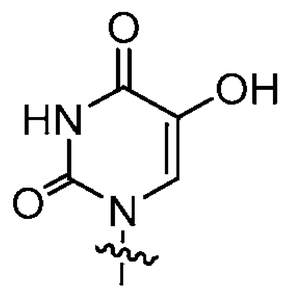
284. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

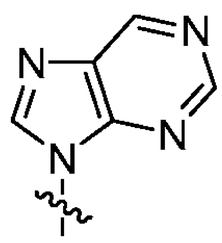
285. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

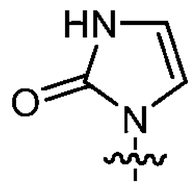
286. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

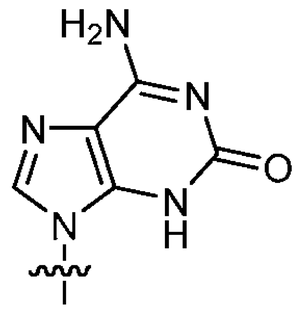
287. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

288. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

289. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

290. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

291. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

292. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

293. The oligonucleotide of any one of Embodiments 143-149, wherein Ring BA is  .

294. The oligonucleotide of any one of Embodiments 143-293, wherein a nucleobase is Ring BA or a tautomer thereof.

295. The oligonucleotide of any one of Embodiments 143-293, wherein a nucleobase is substituted Ring BA or a tautomer thereof.

296. The oligonucleotide of any one of Embodiments 143-293, wherein a nucleobase is optionally substituted Ring BA or a tautomer thereof, wherein each ring −CH=, −CH_2− and −NH− is optionally and independently substituted.

297. The oligonucleotide of any one of Embodiments 143-293, wherein a nucleobase is optionally substituted Ring BA or a tautomer thereof, wherein each ring −CH= and −CH_2− is optionally and independently substituted.

298. The oligonucleotide of any one of Embodiments 143-293, wherein a nucleobase is optionally substituted Ring BA or a tautomer thereof, wherein each ring −CH= is optionally and independently substituted.

299. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F.

300. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the second domain are independently modified sugars with a modification that is not 2'-F.

301. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%,

65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the second domain are independently modified sugars with a modification that is not 2'-F.

302. The oligonucleotide of any one of Embodiments 139-301, wherein the modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

303. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-F modification.

304. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic.

305. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OMe modification.

306. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification, wherein each R is optionally substituted C_{1-6} aliphatic.

307. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification.

308. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) LNA sugars.

309. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

310. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-F modification.

311. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising 2'-OH.

312. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising two 2'-H.

313. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages.

314. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the second domain are modified internucleotidic linkages.

315. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the second domain are modified internucleotidic linkages.

316. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a chiral internucleotidic linkage.

317. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

318. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage.

319. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one or more phosphorothioate internucleotidic linkages.

320. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises 1, 2, 3, 4, or 5 non-negatively charged internucleotidic linkages.

321. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the second domain is a non-negatively charged

internucleotidic linkage.

322. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the second domain is a non-negatively charged internucleotidic linkage.

323. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the second domain is chirally controlled.

324. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the second domain is chirally controlled.

325. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the second domain is chirally controlled.

326. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the second domain is a chirally controlled.

327. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

328. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the second domain is *S*p.

329. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the second domain is *S*p, or wherein each chiral internucleotidic linkages in the second domain is *S*p.

330. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage

between the first and the second nucleosides of the second domain is *R*p.

331. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the second domain is *R*p.

332. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage in the second domain is independently a modified internucleotidic linkage.

333. The oligonucleotide of any one of Embodiments 1-331, wherein the second domain comprises one or more natural phosphate linkages.

334. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain can recruit, or promotes or contributes to recruitment of, an ADAR protein to a target nucleic acid.

335. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain can interact, or promotes or contributes to interaction of, an ADAR protein with a target nucleic acid.

336. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain contacts with a domain that have an enzymatic activity.

337. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain contact with a domain that has a deaminase activity of ADAR1.

338. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain contact with a domain that has a deaminase activity of ADAR2.

339. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises or consists of from the 5' to 3' a first subdomain, a second subdomain , and a third subdomain.

340. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain consists of from the 5' to 3' a first subdomain, a second subdomain , and a third subdomain.

341. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain has a length of about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases.

342. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain has a length of about 10-20 (e.g., about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) nucleobases.

343. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

344. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises two or more mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

345. The oligonucleotide of any one of Embodiments 1-343, wherein the first subdomain comprises one and no more than one mismatch when the oligonucleotide is aligned with a target nucleic acid for complementarity.

346. The oligonucleotide of any one of Embodiments 1-343, wherein the first subdomain comprises two and no more than two mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

347. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges when the oligonucleotide is aligned with a target nucleic acid for complementarity.

348. The oligonucleotide of Embodiment 347, wherein each bulge independently comprises one or more base pairs that are not Watson-Crick or wobble pairs.

349. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

350. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises two or more wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

351. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises two and no more than two wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

352. The oligonucleotide of any one of Embodiments 1-341, wherein the first subdomain is fully complementary to a target nucleic acid.

353. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F.

354. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the first subdomain are independently modified sugars with a modification that is not 2'-F.

355. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%,

90%, 95%, or 100%, etc.) of sugars in the first subdomain are independently modified sugars with a modification that is not 2'-F.

356. The oligonucleotide of any one of Embodiments 353-355, wherein the first subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

357. The oligonucleotide of any one of Embodiments 353-355, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the first subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

358. The oligonucleotide of any one of Embodiments 353-355, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the first subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

359. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification, wherein each R is optionally substituted C_{1-6} aliphatic.

360. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification.

361. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) LNA sugars.

362. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain

comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

363. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-F modification.

364. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising 2'-OH.

365. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising two 2'-H.

366. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic.

367. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OMe modification.

368. The oligonucleotide of any one of Embodiments 339-358, wherein each sugar in the first subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification.

369. The oligonucleotide of Embodiment 368, wherein each sugar in the first subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$.

370. The oligonucleotide of Embodiment 368, wherein each sugar in the first subdomain independently comprises 2'-OMe.

371. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises a 5'-end portion having a length of about 3-8 nucleobases.

372. The oligonucleotide of Embodiment 371, wherein the 5'-end portion has a length of about 3-6 nucleobases.

373. The oligonucleotide of Embodiment 371 or 372, wherein the 5'-end portion comprises the 5'-end nucleobase of the first subdomain.

374. The oligonucleotide of any one of Embodiments 371-373, wherein one or more of the sugars in the 5'-end portion are independently modified sugars.

375. The oligonucleotide of Embodiment 374, wherein the modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally

substituted C_{1-6} aliphatic.

376. The oligonucleotide of Embodiment 374, wherein one or more of the modified sugars independently comprises 2'-F or 2'-OR, wherein R is independently optionally substituted C_{1-6} aliphatic.

377. The oligonucleotide of Embodiment 374, wherein one or more of the modified sugars are independently 2'-F or 2'-OMe.

378. The oligonucleotide of any one of Embodiments 371-377, wherein the 5'-end portion comprises one or more mismatches.

379. The oligonucleotide of any one of Embodiments 371-378, wherein the 5'-end portion comprises one or more wobbles.

380. The oligonucleotide of any one of Embodiments 371-379, wherein the 5'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid.

381. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain comprises a 3'-end portion having a length of about 3-8 nucleobases.

382. The oligonucleotide of Embodiment 381, wherein the 3'-end portion has a length of about 1-3 nucleobases.

383. The oligonucleotide of Embodiment 381 or 382, wherein the 3'-end portion comprises the 3'-end nucleobase of the first subdomain.

384. The oligonucleotide of any one of Embodiments 381-383, wherein one or more of the sugars in the 3'-end portion are independently modified sugars.

385. The oligonucleotide of Embodiment 384, wherein the modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

386. The oligonucleotide of Embodiment 384, wherein one or more of the modified sugars independently comprise 2'-F.

387. The oligonucleotide of any one of Embodiments 384-386, wherein no modified sugars comprise 2'-OMe.

388. The oligonucleotide of any one of Embodiments 381-387, wherein each sugar of the 3'-end portion independently comprises two 2'-H or a 2'-F modification.

389. The oligonucleotide of any one of Embodiments 371-377, wherein the 3'-end portion comprises one or more mismatches.

390. The oligonucleotide of any one of Embodiments 371-378, wherein the 3'-end portion comprises one or more wobbles.

391. The oligonucleotide of any one of Embodiments 371-379, wherein the 3'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid.

392. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain

comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages.

393. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the first subdomain are modified internucleotidic linkages.

394. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the first subdomain are modified internucleotidic linkages.

395. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a chiral internucleotidic linkage.

396. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the first subdomain is a non-negatively charged internucleotidic linkage.

397. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

398. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage.

399. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the first subdomain is chirally controlled.

400. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-

80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the first subdomain is chirally controlled.

401. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the first and the second nucleosides of the first subdomain is chirally controlled.

402. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

403. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the first subdomain is *S*p.

404. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the first subdomain is *S*p.

405. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkages in the first subdomain is *S*p.

406. The oligonucleotide of any one of Embodiments 1-405, wherein the internucleotidic linkage between the first and the second nucleosides of the first subdomain is *R*p.

407. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage in the first subdomain is independently a modified internucleotidic linkage.

408. The oligonucleotide of any one of Embodiments 1-406, wherein the first subdomain comprises one or more natural phosphate linkages.

409. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain can recruit, or promotes or contributes to recruitment of, an ADAR protein to a target nucleic acid.

410. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain can interact, or promotes or contributes to interaction of, an ADAR protein with a target nucleic acid.

411. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain contacts with a domain that have an enzymatic activity.

412. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain contact

with a domain that has a deaminase activity of ADAR1.

413. The oligonucleotide of any one of the preceding Embodiments, wherein the first subdomain contact with a domain that has a deaminase activity of ADAR2.

414. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain has a length of about 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) nucleobases.

415. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain has a length of about 1-5 (e.g., about 1, 2, 3, 4, or 5) nucleobases.

416. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain has a length of about 1, 2, or 3 nucleobases.

417. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain has a length of 3 nucleobases.

418. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises a nucleoside opposite to a target adenosine.

419. The oligonucleotide of any one of the preceding Embodiments, wherein the second domain comprises one and no more than one nucleoside opposite to a target adenosine.

420. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

421. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises two or more mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

422. The oligonucleotide of any one of Embodiments 1-420, wherein the second subdomain comprises one and no more than one mismatch when the oligonucleotide is aligned with a target nucleic acid for complementarity.

423. The oligonucleotide of any one of Embodiments 1-420, wherein the second subdomain comprises two and no more than two mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

424. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges when the oligonucleotide is aligned with a target nucleic acid for complementarity.

425. The oligonucleotide of Embodiment 424, wherein each bulge independently comprises one or more base pairs that are not Watson-Crick or wobble pairs.

426. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

427. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain

comprises two or more wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

428. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises two and no more than two wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

429. The oligonucleotide of any one of Embodiments 1-419, wherein the second subdomain is fully complementary to a target nucleic acid.

430. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises one or more sugars comprising two 2'-H (e.g., natural DNA sugars).

431. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises one or more sugars comprising 2'-OH (e.g., natural RNA sugars).

432. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises about 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) modified sugars.

433. The oligonucleotide of Embodiment 432, wherein each modified sugar is independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

434. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises no modified sugars comprising a 2'-OMe modification.

435. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises no modified sugars comprising a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic.

436. The oligonucleotide of Embodiment 432, wherein each 2'-modified sugar is sugar comprising a 2'-F modification.

437. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside is an acyclic sugar (e.g., a UNA sugar).

438. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside comprises two 2'-H.

439. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside comprises a 2'-OH.

440. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside is a natural DNA sugar.

441. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside comprises is modified.

442. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside comprises 2'-F.

443. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises two 2'-H.

444. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises 2'-OH.

445. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

446. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises 2'-F.

447. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises two 2'-H.

448. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises 2'-OH.

449. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

450. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises 2'-F.

451. The oligonucleotide of any one of Embodiments 1-435, wherein each of the sugar of the opposite nucleoside, the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine), and the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is independently a natural DNA sugar.

452. The oligonucleotide of any one of Embodiments 1-435, wherein the sugar of the opposite nucleoside is a natural DNA sugar, the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-…N_1N_0…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a 2'-F modified sugar, and the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-…N_0N_{-1}…3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

453. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprise a 5'-end portion connected to 5'-side the opposite nucleoside.

454. The oligonucleotide of Embodiment 450, wherein the 5’-end portion comprises one or more mismatches or wobbles when aligned with a target nucleic acid for complementarity.

455. The oligonucleotide of Embodiment 450 or 454, wherein the 5’-end portion has a length of 1, 2 or 3 nucleobases.

456. The oligonucleotide of and one of Embodiments 450-455, wherein sugars of the 5’-end portion are selected from sugars having two 2’-H (e.g., natural DNA sugar) and 2’-F modified sugars.

457. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprise a 3’-end portion connected to the 3’-side of the opposite nucleoside.

458. The oligonucleotide of Embodiment 457, wherein the 3’-end portion comprises one or more mismatches or wobbles when aligned with a target nucleic acid for complementarity.

459. The oligonucleotide of Embodiment 457, wherein the 3’-end portion comprises one or more mismatches and/or wobbles when aligned with a target nucleic acid for complementarity.

460. The oligonucleotide of Embodiment 457, wherein the 3’-end portion comprises one or more wobbles when aligned with a target nucleic acid for complementarity.

461. The oligonucleotide of Embodiment 457, wherein the 3’-end portion comprises an I or a derivative thereof.

462. The oligonucleotide of Embodiment 457, wherein the 3’-end portion comprises an I and an I-C wobble when aligned with a target nucleic acid for complementarity.

463. The oligonucleotide of any one of Embodiments 457-462, wherein the 3’-end portion has a length of 1, 2 or 3 nucleobases.

464. The oligonucleotide of and one of Embodiments 457-463, wherein sugars of the 3’-end portion are selected from sugars having two 2’-H (e.g., natural DNA sugar) and 2’-F modified sugars.

465. The oligonucleotide of and one of Embodiments 457-463, wherein sugars of the 3’-end portion are sugars having two 2’-H (e.g., natural DNA sugar).

466. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprise about 1-10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages.

467. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the second subdomain are modified internucleotidic linkages.

468. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%,

65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the second subdomain are modified internucleotidic linkages.

469. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages in the second subdomain is independently a chiral internucleotidic linkage.

470. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages in the second subdomain is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

471. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages in the second subdomain is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage.

472. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the second subdomain is chirally controlled.

473. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the second subdomain is chirally controlled.

474. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkage in the second subdomain is independently a chirally controlled internucleotidic linkage.

475. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the second subdomain is *S*p.

476. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the

second subdomain is *R*p.

477. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the second subdomain is *S*p.

478. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkages in the second subdomain is *S*p.

479. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage in the second subdomain is independently a modified internucleotidic linkage.

480. The oligonucleotide of any one of Embodiments 1-478, wherein the second subdomain comprises one or more natural phosphate linkages.

481. The oligonucleotide of any one of Embodiments 1-478, wherein the opposite nucleoside is connected to its 5' immediate nucleoside through a natural phosphate linkage.

482. The oligonucleotide of any one of Embodiments 1-480, wherein the opposite nucleoside is connected to its 5' immediate nucleoside through a modified internucleotidic linkage.

483. The oligonucleotide of any one of Embodiments 1-482, wherein the opposite nucleoside is connected to its 3' immediate nucleoside through a modified internucleotidic linkage.

484. The oligonucleotide of any one of Embodiments 1-483, wherein the nucleoside (position -1) that is 3' immediate to an opposite nucleoside (position 0) is connected to its 3' immediate nucleoside (position -2) through a modified internucleotidic linkage.

485. The oligonucleotide of any one of Embodiments 482-484, wherein the modified internucleotidic linkage is a chiral internucleotidic linkage.

486. The oligonucleotide of any one of Embodiments 482-485, wherein the modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

487. The oligonucleotide of any one of Embodiments 482-485, wherein the modified internucleotidic linkage is a non-negatively charged internucleotidic linkage.

488. The oligonucleotide of any one of Embodiments 482-485, wherein the modified internucleotidic linkage is a neutral charged internucleotidic linkage.

489. The oligonucleotide of any one of Embodiments 485-488, wherein the chiral internucleotidic linkage is chirally controlled.

490. The oligonucleotide of any one of Embodiments 485-489, wherein the chiral internucleotidic linkage is *R*p.

491. The oligonucleotide of any one of Embodiments 485-489, wherein the chiral internucleotidic linkage

is *S*p.

492. The oligonucleotide of any one of Embodiments 481-491, wherein the 5’ immediate nucleoside comprises a modified sugar.

493. The oligonucleotide of any one of Embodiments 481-491, wherein the 5’ immediate nucleoside comprises a modified sugar comprising a 2’-F modification.

494. The oligonucleotide of any one of Embodiments 481-491, wherein the 5’ immediate nucleoside comprises a sugar comprising two 2’-H (e.g., a natural DNA sugar).

495. The oligonucleotide of any one of Embodiments 1-478 and 480-494, wherein the opposite nucleoside is connected to its 3’ immediate nucleoside through a natural phosphate linkage.

496. The oligonucleotide of any one of Embodiments 1-478 and 480-494, wherein the opposite nucleoside is connected to its 3’ immediate nucleoside through a modified internucleotidic linkage.

497. The oligonucleotide of Embodiment 496, wherein the modified internucleotidic linkage is a chiral internucleotidic linkage.

498. The oligonucleotide of Embodiment 496 or 497, wherein the modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

499. The oligonucleotide of Embodiment 496 or 497, wherein the modified internucleotidic linkage is a non-negatively charged internucleotidic linkage.

500. The oligonucleotide of Embodiment 496 or 497, wherein the modified internucleotidic linkage is a neutral charged internucleotidic linkage.

501. The oligonucleotide of any one of Embodiments 497-500, wherein the chiral internucleotidic linkage is chirally controlled.

502. The oligonucleotide of any one of Embodiments 497-501, wherein the chiral internucleotidic linkage is *R*p.

503. The oligonucleotide of any one of Embodiments 497-501, wherein the chiral internucleotidic linkage is *S*p.

504. The oligonucleotide of any one of the preceding Embodiments, wherein the 3’ immediate nucleoside comprises a modified sugar.

505. The oligonucleotide of Embodiment 503, wherein the 3’ immediate nucleoside comprises a modified sugar comprising a 2’-F modification.

506. The oligonucleotide of Embodiment 503, wherein the 3’ immediate nucleoside comprises a sugar comprising two 2’-H (e.g., a natural DNA sugar).

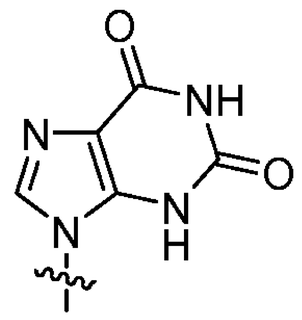
507. The oligonucleotide of any one of the preceding Embodiments, wherein the 3’-immediate nucleoside comprises a base that is not G.

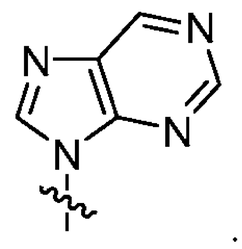
508. The oligonucleotide of any one of the preceding Embodiments, wherein the 3’-immediate nucleoside comprises a base that are less steric than G.

509. The oligonucleotide of any one of the preceding Embodiments, wherein the 3’-immediate nucleoside

comprises a nucleobase which is or comprise Ring BA having the structure of formula BA-VI.

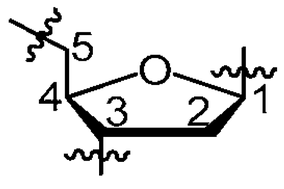
510. The oligonucleotide of any one of Embodiment 507-509, wherein Ring BA is the Ring BA of any one of Embodiments 232-298.

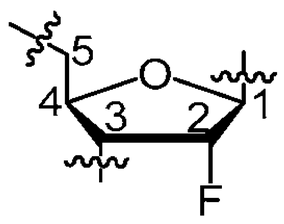
511. The oligonucleotide of any one of Embodiment 507-510, wherein the nucleobase is  .

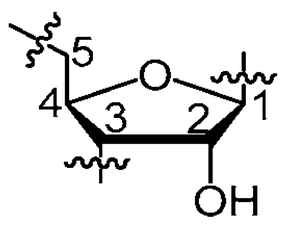
512. The oligonucleotide of any one of Embodiment 507-510, wherein the nucleobase is  .

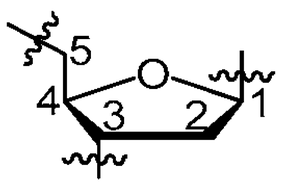
513. The oligonucleotide of any one of Embodiment 507-510, wherein the nucleobase is hypoxanthine.

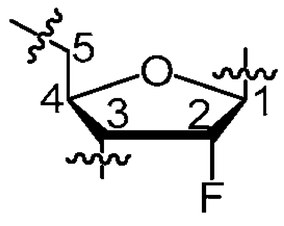
514. The oligonucleotide of any one of the preceding Embodiments, wherein a target nucleic acid comprises 5'-CA-3', wherein A is a target adenosine.

515. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar in a 5' immediate nucleoside is or comprises  .

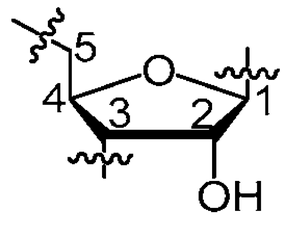
516. The oligonucleotide of any one of Embodiments 1-514, wherein the sugar in a 5' immediate nucleoside is or comprises  .

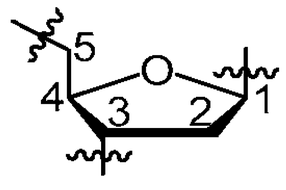
517. The oligonucleotide of any one of Embodiments 1-514, wherein the sugar in a 5' immediate nucleoside is or comprises  .

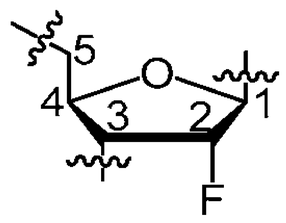
518. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar in a nucleoside opposition to a target nucleoside is or comprises  .

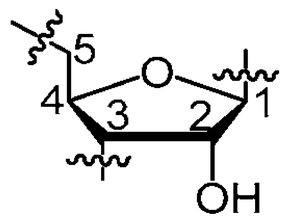
519. The oligonucleotide of any one of Embodiments 1-517, wherein the sugar in a nucleoside opposition to a target nucleoside is or comprises  .

520. The oligonucleotide of any one of Embodiments 1-517, wherein the sugar in a nucleoside opposition

to a target nucleoside is or comprises  .

521. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar in a 3' immediate nucleoside is or comprises  .

522. The oligonucleotide of any one of Embodiments 1-520, wherein the sugar in a 3' immediate nucleoside is or comprises  .

523. The oligonucleotide of any one of Embodiments 1-520, wherein the sugar in a 3'- immediate nucleoside is or comprises  .

524. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain can recruit, or promotes or contributes to recruitment of, an ADAR protein to a target nucleic acid.

525. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain can interact, or promotes or contributes to interaction of, an ADAR protein with a target nucleic acid.

526. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain contacts with a domain that have an enzymatic activity.

527. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain contact with a domain that has a deaminase activity of ADAR1.

528. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain contact with a domain that has a deaminase activity of ADAR2.

529. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain has a length of about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 - about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc.) nucleobases.

530. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain has a length of about 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) nucleobases.

531. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

532. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain

comprises two or more mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

533. The oligonucleotide of any one of Embodiments 1-531, wherein the third subdomain comprises one and no more than one mismatch when the oligonucleotide is aligned with a target nucleic acid for complementarity.

534. The oligonucleotide of any one of Embodiments 1-531, wherein the third subdomain comprises two and no more than two mismatches when the oligonucleotide is aligned with a target nucleic acid for complementarity.

535. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) bulges when the oligonucleotide is aligned with a target nucleic acid for complementarity.

536. The oligonucleotide of Embodiment 535, wherein each bulge independently comprises one or more base pairs that are not Watson-Crick or wobble pairs.

537. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

538. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises two or more wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

539. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises two and no more than two wobble pairs when the oligonucleotide is aligned with a target nucleic acid for complementarity.

540. The oligonucleotide of any one of Embodiments 1-530, wherein the third subdomain is fully complementary to a target nucleic acid.

541. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 – about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently with a modification that is not 2'-F.

542. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the third subdomain are independently modified sugars with a modification that is not 2'-F.

543. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the third subdomain are independently modified sugars with a modification that is not 2'-F.

544. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified sugars independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

545. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the third subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

546. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of sugars in the third subdomain are independently modified sugars selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

547. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-$N(R)_2$ modification, wherein each R is optionally substituted C_{1-6} aliphatic.

548. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain

comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-NH_2 modification.

549. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) LNA sugars.

550. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) acyclic sugars (e.g., UNA sugars).

551. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-F modification.

552. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising 2'-OH.

553. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars comprising two 2'-H.

554. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic.

555. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises one or more (e.g., about 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) modified sugars comprising a 2'-OMe modification.

556. The oligonucleotide of any one of Embodiments 1-546, wherein each sugar in the third subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification.

557. The oligonucleotide of Embodiment 556, wherein each sugar in the third subdomain independently comprises a 2'-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2'−O−L^B−4' modification, wherein L^B is optionally substituted $-CH_2-$.

558. The oligonucleotide of Embodiment 556, wherein each sugar in the third subdomain independently comprises 2'-OMe.

559. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises a 5'-end portion having a length of about 1-8 nucleobases.

560. The oligonucleotide of Embodiment 559, wherein the 5'-end portion has a length of about 1, 2, or 3 nucleobases

561. The oligonucleotide of Embodiment 559 or 560, wherein the 5'-end portion is bonded to the second

subdomain.

562. The oligonucleotide of any one of Embodiments 559-561, wherein one or more of the sugars in the 5'-end portion are independently modified sugars.

563. The oligonucleotide of Embodiment 562, wherein the modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

564. The oligonucleotide of Embodiment 562, wherein one or more of the modified sugars independently comprises 2'-F.

565. The oligonucleotide of any one of Embodiments 559-561, wherein one or more sugars of the 5'-end portion independently comprise two 2'-H (e.g., natural DNA sugar).

566. The oligonucleotide of any one of Embodiments 559-565, wherein one or more sugars of the 5'-end portion independently comprise 2'-OH (e.g., natural RNA sugar).

567. The oligonucleotide of any one of Embodiments 559-561, wherein the sugars of the 5'-end portion independently comprise two 2'-H (e.g., natural DNA sugar) or a 2'-OH (e.g., natural RNA sugar).

568. The oligonucleotide of any one of Embodiments 559-561, wherein the sugars of the 5'-end portion are independently natural DNA or RNA sugars.

569. The oligonucleotide of any one of Embodiments 559-568, wherein the 5'-end portion comprises one or more mismatches.

570. The oligonucleotide of any one of Embodiments 559-569, wherein the 5'-end portion comprises one or more wobbles.

571. The oligonucleotide of any one of Embodiments 559-570, wherein the 5'-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid.

572. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprises a 3'-end portion having a length of about 1-8 nucleobases.

573. The oligonucleotide of Embodiment 572, wherein the 3'-end portion has a length of about 1, 2, 3, or 4 nucleobases.

574. The oligonucleotide of Embodiment 572 or 573, wherein the 3'-end portion comprises the 3'-end nucleobase of the third subdomain.

575. The oligonucleotide of any one of Embodiments 572-574, wherein one or more of the sugars in the 3'-end portion are independently modified sugars.

576. The oligonucleotide of Embodiment 575, wherein the modified sugars are independently selected from a bicyclic sugar (e.g., a LNA sugar), an acyclic sugar (e.g., a UNA sugar), a sugar with a 2'-OR modification, or a sugar with a 2'-$N(R)_2$ modification, wherein each R is independently optionally substituted C_{1-6} aliphatic.

577. The oligonucleotide of any one of Embodiments 575-576, wherein one or more modified sugars

independently comprises 2’-F.

578. The oligonucleotide of any one of Embodiments 575-576, wherein at least 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 95% sugars in the third subdomain independently comprise 2’-F.

579. The oligonucleotide of any one of Embodiments 575-578, wherein one or more sugars in the 3’-end portion independently comprise a 2’-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2’−O−L^B−4’ modification.

580. The oligonucleotide of Embodiment 579, wherein each sugar in the 3’-end portion independently comprises a 2’-OR modification, wherein R is optionally substituted C_{1-6} aliphatic, or a 2’−O−L^B−4’ modification.

581. The oligonucleotide of any one of Embodiments 579-580, wherein L^B is optionally substituted −CH_2−.

582. The oligonucleotide of any one of Embodiments 579-580, wherein L^B is −CH_2−.

583. The oligonucleotide of Embodiment 579, wherein each sugar in the 3’-end portion independently comprises 2’-OMe.

584. The oligonucleotide of any one of Embodiments 572-583, wherein the 3’-end portion comprises one or more mismatches.

585. The oligonucleotide of any one of Embodiments 572-584, wherein the 3’-end portion comprises one or more wobbles.

586. The oligonucleotide of any one of Embodiments 572-585, wherein the 3’-end portion is about 60-100% (e.g., 66%, 70%, 75%, 80%, 85%, 90%, 95%, or more) complementary to a target nucleic acid.

587. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain comprise about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) modified internucleotidic linkages.

588. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the third subdomain are modified internucleotidic linkages.

589. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-

100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of internucleotidic linkages in the third subdomain are modified internucleotidic linkages.

590. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a chiral internucleotidic linkage.

591. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the third subdomain is a non-negatively charged internucleotidic linkage.

592. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

593. The oligonucleotide of any one of the preceding Embodiments, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a neutral internucleotidic linkage.

594. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the third subdomain is chirally controlled.

595. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the third subdomain is chirally controlled.

596. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between the last and the second last nucleosides of the third subdomain is chirally controlled.

597. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkage is independently a chirally controlled internucleotidic linkage.

598. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 1-50 (e.g., about 5, 6, 7, 8, 9, or 10 − about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, or about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50, etc., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) chiral internucleotidic linkages in the third subdomain is *S*p.

599. The oligonucleotide of any one of the preceding Embodiments, wherein at least 5%-100% (e.g.,

about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of chiral internucleotidic linkages in the third subdomain is *S*p.

600. The oligonucleotide of any one of the preceding Embodiments, wherein each chiral internucleotidic linkages in the third subdomain is *S*p.

601. The oligonucleotide of any one of Embodiments 1-599, wherein the internucleotidic linkage between the last and the second lase nucleosides of the third subdomain is *R*p.

602. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage linking the last nucleoside of the second subdomain and the first nucleoside of the third subdomain is a non-negatively charged internucleotidic linkage.

603. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage at position -2 is a non-negatively charged internucleotidic linkage.

604. The oligonucleotide of any one of Embodiments 602-603, wherein the non-negatively charged internucleotidic linkage is chirally controlled.

605. The oligonucleotide of Embodiment 604, wherein the non-negatively charged internucleotidic linkage is *R*p.

606. The oligonucleotide of Embodiment 604, wherein the non-negatively charged internucleotidic linkage is *S*p.

607. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage in the third subdomain is independently a modified internucleotidic linkage.

608. The oligonucleotide of any one of Embodiments 1-606, wherein the third subdomain comprises one or more natural phosphate linkages.

609. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain can recruit, or promotes or contributes to recruitment of, an ADAR protein to a target nucleic acid.

610. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain can interact, or promotes or contributes to interaction of, an ADAR protein with a target nucleic acid.

611. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain contacts with a domain that have an enzymatic activity.

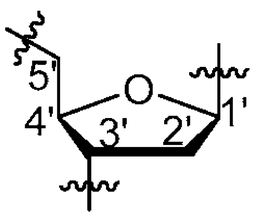
612. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain contact with a domain that has a deaminase activity of ADAR1.

613. The oligonucleotide of any one of the preceding Embodiments, wherein the third subdomain contact with a domain that has a deaminase activity of ADAR2.

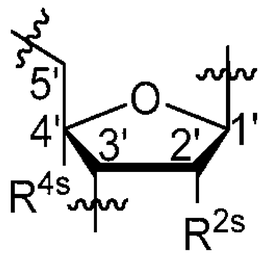
614. The oligonucleotide of any one of the preceding Embodiments, wherein each wobble base pair is

independently G-U, I-A, G-A, I-U, I-C, I-T, A-A, or reverse A-T.

615. The oligonucleotide of any one of the preceding Embodiments, wherein each wobble base pair is independently G-U, I-A, G-A, I-U, or I-C.

616. The oligonucleotide of any one of the preceding Embodiments, wherein each cyclic sugar or each sugar is independently optionally substituted 

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617. The oligonucleotide of any one of the preceding Embodiments, wherein each cyclic sugar or each sugar independently has the structure of 

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618. The oligonucleotide of Embodiment 617, wherein the oligonucleotide comprises one or more sugars wherein R^{2s} and R^{4s} are H.

619. The oligonucleotide of any one of Embodiments 617-618, wherein the oligonucleotide comprises one or more sugars wherein R^{2s} is −OR, and R^{4s} is H.

620. The oligonucleotide of any one of Embodiments 617-619, wherein the oligonucleotide comprises one or more sugars wherein R^{2s} is −OR, wherein R is optionally substituted C_{1-4} alkyl and R^{4s} is H.

621. The oligonucleotide of any one of Embodiments 617-620, wherein the oligonucleotide comprises one or more sugars wherein R^{2s} is −OMe and R^{4s} is H.

622. The oligonucleotide of any one of Embodiments 617-621, wherein the oligonucleotide comprises one or more sugars wherein R^{2s} is −F and R^{4s} is H.

623. The oligonucleotide of any one of Embodiments 617-622, wherein the oligonucleotide comprises one or more sugars wherein R^{4s} and R^{2s} are forming a bridge having the structure of optionally substituted 2'−O−CH_2−4'.

624. The oligonucleotide of any one of Embodiments 617-622, wherein the oligonucleotide comprises one or more sugars wherein R^{4s} and R^{2s} are forming a bridge having the structure of 2'−O−CH_2−4'.

625. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises an additional chemical moiety.

626. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises a targeting moiety.

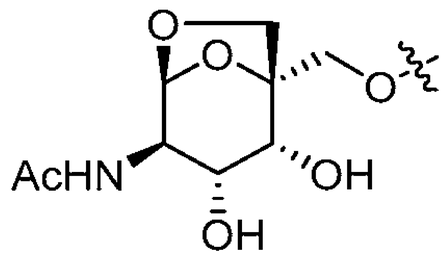
627. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises a carbohydrate moiety.

628. The oligonucleotide of any one of Embodiments 623-627, wherein the moiety is or comprises a ligand for an asialoglycoprotein receptor.

629. The oligonucleotide of any one of Embodiments 623-628, wherein the moiety is or comprises

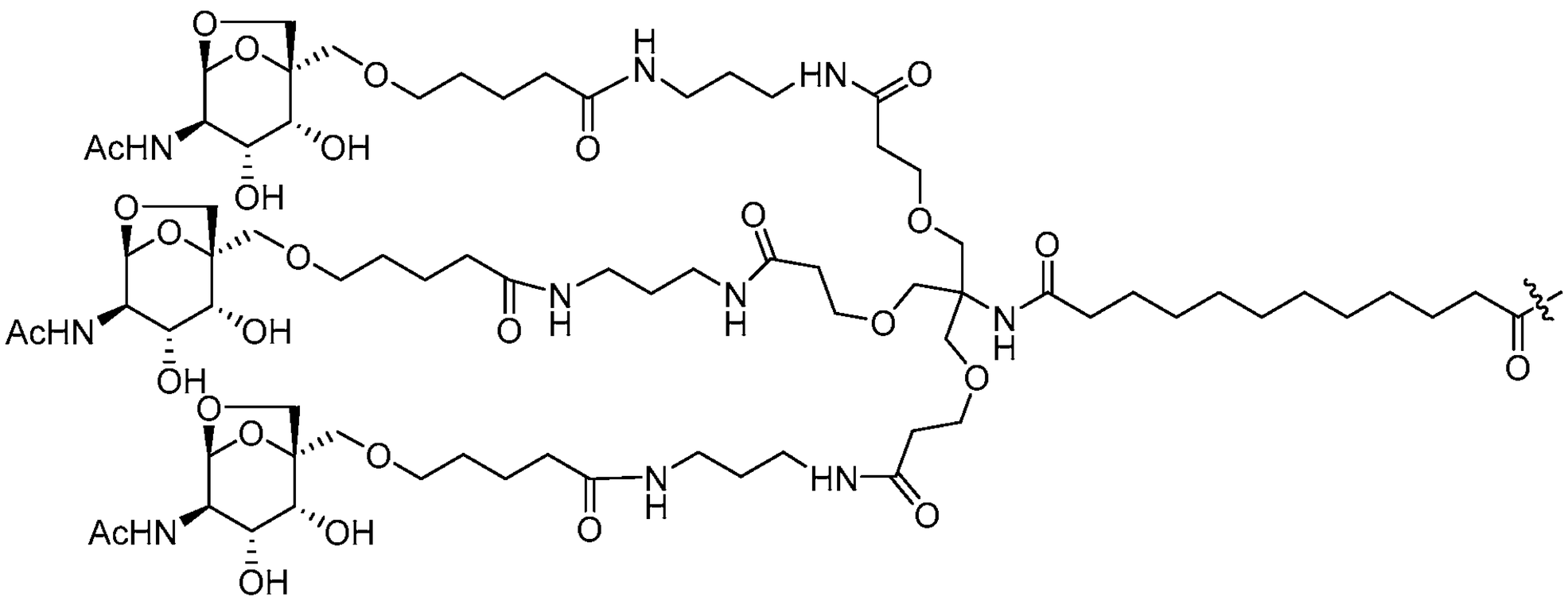
GalNAc or a derivative thereof.

630. The oligonucleotide of any one of Embodiments 623-629, wherein the moiety is or comprises



optionally substituted .

631. The oligonucleotide of any one of Embodiments 623-629, wherein the moiety is or comprises optionally substituted



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632. The oligonucleotide of any one of Embodiments 623-631, wherein the moiety is connected to an oligonucleotide chain through a linker.

633. The oligonucleotide of Embodiment 632, wherein the linker is or comprises L001.

634. The oligonucleotide of Embodiment 633, wherein L001 is connected to 5'-end 5'-carbon of an oligonucleotide chain through a phosphate group

635. The oligonucleotide of any one of the preceding Embodiments, wherein an additional chemical moiety is or comprises a nucleic acid moiety.

636. The oligonucleotide of Embodiment 635, wherein the nucleic acid is or comprises an aptamer.

637. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in a salt form.

638. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in a pharmaceutically acceptable salt form.

639. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in a sodium salt form.

640. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in an ammonium salt form.

641. The oligonucleotide of any one of the preceding Embodiments, wherein if any, at least one or each neutral internucleotidic linkage is independently n001.

642. The oligonucleotide of any one of the preceding Embodiments, wherein if any, each non-negatively charged internucleotidic linkage is independently n001.

643. The oligonucleotide of any one of the preceding Embodiments, wherein no more than 5, 6, 7, 8, 9, 10, 11 or 12 nucleosides 3' to a nucleoside opposite to a target adenosine.

644. The oligonucleotide of any one of the preceding Embodiments, wherein no more than 5, 6, 7, 8, 9, 10, 11 or 12 nucleosides 3' to a nucleoside opposite to a target nucleoside, wherein each of the nucleosides is independently optionally substituted A, T, C, G, U, or a tautomer thereof.

645. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%) of internucleotidic linkages 3' to a nucleoside opposite to a target adenosine are each independently a modified internucleotidic linkage.

646. The oligonucleotide of any one of the preceding Embodiments, wherein about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%) of internucleotidic linkages 3' to a nucleoside opposite to a target adenosine are each independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

647. The oligonucleotide of any one of the preceding Embodiments, wherein no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target adenosine are natural phosphate linkages.

648. The oligonucleotide of any one of the preceding Embodiments, wherein no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target adenosine are *R*p internucleotidic linkages.

649. The oligonucleotide of any one of the preceding Embodiments, wherein no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target adenosine are *R*p phosphorothioate internucleotidic linkages.

650. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between a nucleoside opposite to a target nucleoside and its 3' immediate nucleoside (considered a -1 position) is a stereorandom phosphorothioate internucleotidic linkage.

651. The oligonucleotide of any one of Embodiments 1-649, wherein the internucleotidic linkage between a nucleoside opposite to a target nucleoside and its 3' immediate nucleoside (considered a -1 position) is a chirally controlled *R*p phosphorothioate internucleotidic linkage.

652. The oligonucleotide of any one of Embodiments 1-649, wherein the internucleotidic linkage between a nucleoside opposite to a target nucleoside and its 3' immediate nucleoside (considered a -1 position) is a chirally controlled *S*p phosphorothioate internucleotidic linkage

653. The oligonucleotide of any one of Embodiments 1-649, wherein an internucleotidic linkage bonded to a nucleoside opposite to a target nucleoside at the 3'-position of its sugar (considered a -1 position) is a *R*p phosphorothioate internucleotidic linkage, and optionally the only *R*p phosphorothioate internucleotidic linkage 3' to a nucleoside opposite to a target adenosine.

654. The oligonucleotide of any one of Embodiments 1-649, wherein an internucleotidic linkage bonded to a nucleoside opposite to a target nucleoside at the 3'-position of its sugar (considered a -1 position) is a *S*p

phosphorothioate internucleotidic linkage.

655. The oligonucleotide of any one of Embodiments 1-649, wherein an internucleotidic linkage bonded to a nucleoside opposite to a target nucleoside at the 3'-position of its sugar (considered a -1 position) is a stereorandom phosphorothioate internucleotidic linkage.

656. The oligonucleotide of any one of Embodiments 1-649, wherein the internucleotidic linkage between a 3' immediate nucleoside of a nucleoside opposite to a target nucleoside and the next 3' immediate nucleoside (e.g., position -2 between N_{-1} and N_{-2} of 5'-…$N_0N_{-1}N_{-2}$…-3' wherein N_0 represents a nucleoside opposite to a target nucleoside) is a non-negatively charged internucleotidic linkage.

657. The oligonucleotide of Embodiment 656, wherein the non-negatively charged internucleotidic linkage is stereorandom.

658. The oligonucleotide of Embodiment 656, wherein the non-negatively charged internucleotidic linkage is chirally controlled.

659. The oligonucleotide of Embodiment 656, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *S*p.

660. The oligonucleotide of Embodiment 656, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *R*p.

661. The oligonucleotide of any one of Embodiments 656-660, wherein a non-negatively charged internucleotidic linkage is phosphoryl guanidine internucleotidic linkage.

662. The oligonucleotide of any one of Embodiments 656-660, wherein a non-negatively charged internucleotidic linkage is n001.

663. The oligonucleotide of any one of Embodiments 656-660, wherein a non-negatively charged internucleotidic linkage is n004, n008, n025 or n026.

664. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage is a non-negatively charged internucleotidic linkage.

665. The oligonucleotide of Embodiment 664, wherein the non-negatively charged internucleotidic linkage is stereorandom.

666. The oligonucleotide of Embodiment 664, wherein the non-negatively charged internucleotidic linkage is chirally controlled.

667. The oligonucleotide of Embodiment 664, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *S*p.

668. The oligonucleotide of Embodiment 664, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *R*p.

669. The oligonucleotide of any one of Embodiments 664-668, wherein a non-negatively charged internucleotidic linkage is phosphoryl guanidine internucleotidic linkage.

670. The oligonucleotide of any one of Embodiments 664-668, wherein a non-negatively charged internucleotidic linkage is n001.

671. The oligonucleotide of any one of Embodiments 664-668, wherein a non-negatively charged internucleotidic linkage is n004, n008, n025, n026.

672. The oligonucleotide of any one of the preceding Embodiments, wherein the last internucleotidic linkage is a non-negatively charged internucleotidic linkage.

673. The oligonucleotide of Embodiment 672, wherein the non-negatively charged internucleotidic linkage is stereorandom.

674. The oligonucleotide of Embodiment 672, wherein the non-negatively charged internucleotidic linkage is chirally controlled.

675. The oligonucleotide of Embodiment 672, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *S*p.

676. The oligonucleotide of Embodiment 672, wherein the non-negatively charged internucleotidic linkage is chirally controlled and is *R*p.

677. The oligonucleotide of any one of Embodiments 672-676, wherein a non-negatively charged internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage.

678. The oligonucleotide of any one of Embodiments 672-676, wherein a non-negatively charged internucleotidic linkage is n004, n008, n025, n026.

679. The oligonucleotide of any one of Embodiments 672-676, wherein a non-negatively charged internucleotidic linkage is n001.

680. The oligonucleotide of any one of the preceding Embodiments, wherein an internucleotidic linkage at position -3 relative to a nucleoside opposite to a target adenosine is not a *R*p phosphorothioate internucleotidic linkage.

681. The oligonucleotide of any one of the preceding Embodiments, wherein an internucleotidic linkage at position -6 relative to a nucleoside opposite to a target adenosine is not a *R*p phosphorothioate internucleotidic linkage.

682. The oligonucleotide of any one of the preceding Embodiments, wherein an internucleotidic linkage at position -4 and/or -5 relative to a nucleoside opposite to a target nucleoside is a modified internucleotidic linkage, e.g., a phosphorothioate internucleotidic linkage.

683. The oligonucleotide of any one of the preceding Embodiments, wherein a nucleoside opposite to a target nucleoside is at position 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more from the 5'-end.

684. The oligonucleotide of any one of the preceding Embodiments, wherein a nucleoside opposite to a target nucleoside is at position 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more from the 3'-end.

685. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 4.

686. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 5.

687. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 6.

688. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 7.

689. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 8.

690. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 9.

691. The oligonucleotide of Embodiment 683 or 684, wherein the position is position 10.

692. The oligonucleotide of any one of the preceding Embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of internucleotidic linkages 5' to a nucleoside opposite to a target adenosine are each independently a modified internucleotidic linkage, which is optionally chirally controlled.

693. The oligonucleotide of any one of the preceding Embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each chirally controlled and are *S*p.

694. The oligonucleotide of any one of the preceding Embodiments, wherein no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target adenosine are natural phosphate linkages

695. The oligonucleotide of any one of the preceding Embodiments, an internucleotidic linkage at position +5 relative to a nucleoside opposite to a target nucleoside (e.g., for …$N_{+5}N_{+4}N_{+3}N_{+2}N_{+1}N_0$…, the internucleotidic linkage linking N_{+4} and N_{+5} wherein N_0 is a nucleoside opposite to a target nucleoside) is not a *R*p phosphorothioate internucleotidic linkage.

696. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all internucleotidic linkages at positions +6 to +8 relative to a nucleoside opposite to a target adenosine are each independently a modified internucleotidic linkage, optionally chirally controlled.

697. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all internucleotidic linkages at positions +6 to +8 relative to a nucleoside opposite to a target adenosine are each independently a phosphorothioate internucleotidic linkage, optionally chirally controlled.

698. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all internucleotidic linkages at positions +6, +7, +8, +9, and +11 relative to a nucleoside opposite to a target adenosine are each independently *R*p phosphorothioate internucleotidic linkages.

699. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all internucleotidic linkages at positions +5, +6, +7, +8, and +9 relative to a nucleoside opposite to a target adenosine are each independently *S*p phosphorothioate internucleotidic linkages.

700. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a complementarity of about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, or at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) to a PiZZ allele (e.g.,

atcgacAagaaagggactgaagc).

701. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa.

702. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

703. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UCCCUUUCTCIUCGA.

704. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UCCCUUUCTCGUCGA.

705. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa.

706. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

707. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UCCCUUUCTCIUCGA.

708. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UCCCUUUCTCGUCGA.

709. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UUCAGUCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa.

710. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

711. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UUCAGUCCCUUUCTCIUCGA.

712. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UUCAGUCCCUUUCTCGUCGA.

713. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the

oligonucleotide is or comprises UUCAGUCCCUUUCTCIUCGA, wherein each U can be independently replaced with T and vice versa.

714. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

715. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UUCAGUCCCUUUCTCIUCGA.

716. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises UUCAGUCCCUUUCTCGUCGA.

717. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

718. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

719. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA.

720. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA.

721. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

722. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

723. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, wherein each U can be independently replaced with T and vice versa.

724. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA.

725. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA.

726. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

727. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

728. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

729. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

730. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

731. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

732. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

733. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

734. The oligonucleotide of any one of the preceding Embodiments, wherein the base sequence of the oligonucleotide is CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

735. The oligonucleotide of any one of Embodiments 1-724, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

736. The oligonucleotide of any one of Embodiments 1-724, wherein the base sequence of the oligonucleotide is CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU.

737. The oligonucleotide of any one of Embodiments 1-724, wherein the base sequence of the oligonucleotide is or comprises CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU.

738. The oligonucleotide of any one of Embodiments 1-724, wherein the base sequence of the oligonucleotide is CCCAGCAGCUUCAGUCCCUUUCUAIUCGAU.

739. The oligonucleotide of any one of the preceding Embodiments, comprising an optionally protected

nucleobase of a nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, and zdnp.

740. The oligonucleotide of any one of the preceding Embodiments, comprising an optionally protected nucleobase of a nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, and b007C.

741. An oligonucleotide, comprising an optionally protected nucleobase of a nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, and zdnp.

742. An oligonucleotide, comprising an optionally protected nucleobase of a nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, and b007C.

743. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b001U.

744. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b002U.

745. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b003U.

746. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b004U.

747. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b005U.

748. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b006U.

749. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b007U.

750. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b008U.

751. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b009U.

752. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b011U.

753. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b012U.

754. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected

nucleobase b013U.

755. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b001A.

756. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b002A.

757. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b003A.

758. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b001G.

759. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b002G.

760. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b001C.

761. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b002C.

762. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b003C.

763. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b004C.

764. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b005C.

765. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b006C.

766. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b007C.

767. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b008C.

768. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b009C.

769. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b002I.

770. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b003I.

771. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase b004I.

772. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected

nucleobase b014I.

773. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleobase and zdnp.

774. The oligonucleotide of any one of the preceding Embodiments, comprising an optionally protected nucleoside selected from aC, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b010U, b011U, b012U, b013U, b001A, b001rA, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b003mC, b004C, b005C, b006C, b007C, b008C, b002I, b003I, b004I, b014I, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm04, Csm11, Gsm11, Tsm11, b009Csm11, b009Csm12, Gsm12, Tsm12, Csm12, rCsm13, rCsm14, Csm15, Csm16, Csm17, L034, zdnp, and Tsm18.

775. The oligonucleotide of any one of the preceding Embodiments, comprising an optionally protected nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, b007C, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm15, Csm16, rCsm14, Csm17 and Tsm18.

776. An oligonucleotide, comprising an optionally protected nucleoside selected from aC, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b010U, b011U, b012U, b013U, b001A, b001rA, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b003mC, b004C, b005C, b006C, b007C, b008C, b002I, b003I, b004I, b014I, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm04, Csm11, Gsm11, Tsm11, b009Csm11, b009Csm12, Gsm12, Tsm12, Csm12, rCsm13, rCsm14, Csm15, Csm16, Csm17, L034, zdnp, and Tsm18.

777. An oligonucleotide, comprising an optionally protected nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, b007C, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm15, Csm16, rCsm14, Csm17 and Tsm18.

778. The oligonucleotide of any one of the preceding Embodiments, comprising an optionally protected sugar of a nucleoside selected from Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm15, Csm16, rCsm14, Csm17 and Tsm18.

779. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside aC.

780. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b001U.

781. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b002U.

782. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b003U.

783. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b004U.

784. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b005U.

785. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b006U.

786. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b007U.

787. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b008U.

788. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b009U.

789. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b010U.

790. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b011U.

791. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b012U.

792. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b013U.

793. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b001A.

794. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b001rA.

795. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b002A.

796. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b003A.

797. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b001G.

798. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b002G.

799. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b001C.

800. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b002C.

801. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b003C.

802. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b003mC.

803. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b004C.

804. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b005C.

805. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b006C.

806. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b007C.

807. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b008C.

808. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b002I.

809. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b003I.

810. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b004I.

811. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b014I.

812. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Asm01.

813. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Gsm01.

814. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside 5MSfC.

815. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Usm04.

816. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside 5MRdT.

817. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm04.

818. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm11.

819. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Gsm11.

820. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Tsm11.

821. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b009Csm11.

822. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside b009Csm12.

823. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Gsm12.

824. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Tsm12.

825. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm12.

826. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside rCsm13.

827. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside rCsm14.

828. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm15.

829. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm16.

830. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Csm17.

831. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected abasic nucleoside.

832. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected L010.

833. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside L034.

834. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside zdnp.

835. The oligonucleotide of any one of the preceding Embodiments, comprising optionally protected nucleoside Tsm18.

836. The oligonucleotide of any one of the preceding Embodiments, wherein each optionally protected nucleobase or nucleoside is independently an optionally substituted nucleobase or nucleoside, respectively.

837. The oligonucleotide of any one of the preceding Embodiments, wherein each optionally protected or substituted nucleobase or nucleoside is not protected or substituted, respectively.

838. The oligonucleotide of any one of the preceding Embodiments, comprising an internucleotidic linkage having the structure of −Y−P(=W)(−X−R^L)−Z−.

839. An oligonucleotide, comprising an internucleotidic linkage having the structure of −Y−P(=W)(−X−R^L)−Z−.

840. The oligonucleotide of Embodiment 838 or 839, wherein W is O.

841. The oligonucleotide of Embodiment 838 or 839, wherein W is S.

842. The oligonucleotide of any one of Embodiments 838-841, wherein Y is −O−.

843. The oligonucleotide of any one of Embodiments 838-842, wherein Z is a covalent bond.

844. The oligonucleotide of any one of Embodiments 838-842, wherein Z is −O−.

845. An oligonucleotide, comprising an internucleotidic linkage comprising −X−R^L.

846. The oligonucleotide of any one of the preceding Embodiments, comprising an internucleotidic linkage comprising −X−R^L.

847. The oligonucleotide of any one of Embodiments 838-846, wherein −X−R^L is −N(R')SO_2R", wherein R" is R', −OR', or −N(R')$_2$.

848. The oligonucleotide of any one of Embodiments 838-846, wherein −X−R^L is −NHSO_2R", wherein R" is optionally substituted C_{1-6} aliphatic.

849. The oligonucleotide of any one of Embodiments 838-846, wherein −X−R^L is −NHSO_2R", wherein R" is methyl.

850. The oligonucleotide of any one of Embodiments 838-846, wherein −X−R^L is −NHSO_2R", wherein R" is optionally substituted phenyl.

851. The oligonucleotide of any one of the preceding Embodiments, comprising n002.

852. The oligonucleotide of any one of the preceding Embodiments, comprising n006.

853. The oligonucleotide of any one of the preceding Embodiments, comprising n020.

854. The oligonucleotide of any one of the preceding Embodiments, comprising −OP(=O)(NHSO_2CH_3)O−.

855. The oligonucleotide of any one of the preceding Embodiments, wherein the first one, two, or three internucleotidic linkages are each independently an internucleotidic linkage of any one of Embodiments 847-854.

856. The oligonucleotide of any one of the preceding Embodiments, wherein the last one, two, or three internucleotidic linkages are each independently an internucleotidic linkage of any one of Embodiments 847-854.

857. The oligonucleotide of any one of the preceding Embodiments, wherein one or more internal internucleotidic linkages are each independently an internucleotidic linkage of any one of Embodiments 847-854.

858. The oligonucleotide of any one of Embodiments 838-846, wherein −X−R^L is −N(R')C(O)R", wherein R" is R', −OR', or −N(R')$_2$.

859. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-NHC(O)R''$, wherein R'' is optionally substituted C_{1-6} aliphatic.

860. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-NHC(O)R''$, wherein R'' is methyl.

861. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-NHC(O)R''$, wherein R'' is optionally substituted phenyl.

862. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-NHC(O)R''$, wherein R'' is $-OR'$.

863. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-NHC(O)R''$, wherein R'' is $-N(R')_2$.

864. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-N(R')P(O)(R'')_2$, wherein each R'' is independently R', $-OR'$, or $-N(R')_2$.

865. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is $-N(R')P(S)(R'')_2$, wherein each R'' is independently R', $-OR'$, or $-N(R')_2$.

866. The oligonucleotide of any one of Embodiments 838-846, wherein $-X-R^L$ is selected from Table L-1, L-2, L-3, L-4, L-5 or L-6.

867. The oligonucleotide of any one of the preceding Embodiments, wherein about 20%-90% (e.g., about 20%-80%, 20%-70%, 30%-90%, 30%-80%, 30%-70%, 30%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are 2'-F modified sugars.

868. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are 2'-F modified sugars.

869. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% (e.g., about 40%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are 2'-F modified sugars.

870. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 65% of all sugars of the oligonucleotide are 2'-F modified sugars.

871. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 70% of all sugars of the oligonucleotide are 2'-F modified sugars.

872. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 75% of all sugars of the oligonucleotide are 2'-F modified sugars.

873. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 80% of all sugars of the oligonucleotide are 2'-F modified sugars.

874. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 85% of all sugars of the oligonucleotide are 2'-F modified sugars.

875. The oligonucleotide of any one of the preceding Embodiments, wherein at least about 90% of all

sugars of the oligonucleotide are 2'-F modified sugars.

876. The oligonucleotide of any one of the preceding Embodiments, wherein about 20%-90% (e.g., about 20%-80%, 20%-70%, 30%-90%, 30%-80%, 30%-70%, 30%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are each independently 2'-OR modified sugars wherein R is not –H.

877. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-70% (e.g., about 30%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are each independently 2'-OR modified sugars wherein R is not –H..

878. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% (e.g., about 40%-60%, 30%-50%, about 30%, 40%, 50%, 60% or 70%) of all sugars of the oligonucleotide are each independently 2'-OR modified sugars wherein R is not –H.

879. The oligonucleotide of any one of Embodiments 876-878, wherein a 2'-OR modified sugar is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

880. The oligonucleotide of any one of the preceding Embodiments, wherein a 2'-OR modified sugar is a 2'-OMe modified sugar.

881. The oligonucleotide of any one of the preceding Embodiments, wherein a 2'-OR modified sugar is a 2'-MOE modified sugar.

882. The oligonucleotide of any one of the preceding Embodiments, wherein a 2'-OR modified sugar is a bicyclic sugar.

883. The oligonucleotide of any one of the preceding Embodiments, wherein a 2'-OR modified sugar is a LNA sugar.

884. The oligonucleotide of any one of the preceding Embodiments, wherein a 2'-OR modified sugar is a cEt sugar.

885. The oligonucleotide of any one of Embodiments 876-878, wherein each 2'-OR modified sugar is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

886. The oligonucleotide of any one of Embodiments 876-878, wherein each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar.

887. The oligonucleotide of any one of Embodiments 876-878, wherein each 2'-OR modified sugar is independently a 2'-OMe or 2'-MOE modified sugar, wherein at least one is a 2'-OMe modified sugar and at least one is a 2'-MOE modified sugar.

888. The oligonucleotide of any one of Embodiments 876-878, wherein each 2'-OR modified sugar is a 2'-OMe modified sugar.

889. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain comprises one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F blocks and one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.)

separating blocks, wherein each sugar in each 2’-F block is independently a 2’-F modified sugar, and wherein each sugar in each separating block is independently a sugar other than a 2’-F modified sugar.

890. The oligonucleotide of any one of the preceding Embodiments, wherein there are 2 or more 2’-F blocks in the first domain.

891. The oligonucleotide of any one of the preceding Embodiments, wherein there are 3 or more 2’-F blocks in the first domain.

892. The oligonucleotide of any one of the preceding Embodiments, wherein there are 4 or more 2’-F blocks in the first domain.

893. The oligonucleotide of any one of the preceding Embodiments, wherein there are 5 or more 2’-F blocks in the first domain.

894. The oligonucleotide of any one of the preceding Embodiments, wherein there are 2 or more separating blocks in the first domain.

895. The oligonucleotide of any one of the preceding Embodiments, wherein there are 3 or more separating blocks in the first domain.

896. The oligonucleotide of any one of the preceding Embodiments, wherein there are 4 or more separating blocks in the first domain.

897. The oligonucleotide of any one of the preceding Embodiments, wherein there are 5 or more separating blocks in the first domain.

898. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in each separating block is independently a 2’-modified sugar.

899. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar in a separating block is independently a 2’-OR sugar wherein R is not −H.

900. The oligonucleotide of any one of the preceding Embodiments, wherein each separating block independently comprises a 2’-OR modified sugar wherein R is not −H.

901. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar in a separating block is independently a 2’-OR sugar wherein R is optionally substituted C_{1-6} aliphatic.

902. The oligonucleotide of any one of the preceding Embodiments, wherein each separating block independently comprises a 2’-OR modified sugar wherein R optionally substituted C_{1-6} aliphatic.

903. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in each separating block is independently a 2’-OR modified sugar or a bicyclic sugar, wherein R is optionally substituted C_{1-6} aliphatic.

904. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in a separating block is independently a 2’-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

905. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in each separating block is independently a 2’-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

906. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in a separating

block is independently a 2'-OMe or 2'-MOE modified sugar.

907. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in each separating block is independently a 2'-OMe or 2'-MOE modified sugar.

908. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar in a separating block is a 2'-OME modified sugar.

909. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in a separating block is independently a 2'-OMe modified sugar.

910. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar in a separating block is independently a 2'-MOE modified sugar.

911. The oligonucleotide of any one of Embodiments 1-897, wherein each sugar in each separating block is independently a 2'-OMe modified sugar.

912. The oligonucleotide of any one of Embodiments 1-897, wherein each sugar in each separating block is independently a 2'-MOE modified sugar.

913. The oligonucleotide of any one of Embodiments 889-912, wherein in each 2'-F block there are independently about 1-20 (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F modified sugars.

914. The oligonucleotide of any one of Embodiments 889-912, wherein in each 2'-F block there are about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 2'-F modified sugars.

915. The oligonucleotide of any one of Embodiments 889-912, wherein in each 2'-F block there are about 1, 2, 3, 4 or 5 2'-F modified sugars.

916. The oligonucleotide of any one of Embodiments 889-912, wherein in each 2'-F block there are about 1, 2, or 3 2'-F modified sugars.

917. The oligonucleotide of any one of Embodiments 889-916, wherein in each separating block there are independently about 1-20 (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) sugars.

918. The oligonucleotide of any one of Embodiments 889-916, wherein in each separating block there are about 1-10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 sugars.

919. The oligonucleotide of any one of Embodiments 889-916, wherein in each separating block there are about 1, 2, 3, 4 or 5 sugars.

920. The oligonucleotide of any one of Embodiments 889-916, wherein in each separating there are about 1, 2, or 3 sugars.

921. The oligonucleotide of any one of Embodiments 889-920, wherein each block in a first domain that is bonded to a 2'-F block in a first domain is a separating block.

922. The oligonucleotide of any one of Embodiments 889-921, wherein each block in a first domain that is bonded to a separating block in a first domain is a 2'-F block.

923. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide

comprises two or more 2'-F modified sugar blocks, wherein each 2'-F modified sugar block independently comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive 2'-F modified sugars, wherein each two consecutive 2'-F modified sugar blocks are independently separated by a separating block which separating block comprises one or more sugars that are independently not 2'-F modified sugars and no consecutive 2'-F modified sugars.

924. The oligonucleotide of any one of the preceding Embodiments, wherein at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% (e.g., 50%-100%, 60%-100%, 70-100%, 75%-100%, 80%-100%, 90%-100%, 95%-100%, 60%-95%, 70%-95%, 75-95%, 80-95%, 85-95%, 90-95%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, etc.) of all, or all phosphorothioate internucleotidic linkages, are *S*p.

925. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain is at the 5' side of a second domain.

926. The oligonucleotide of any one of the preceding Embodiments, wherein the first domain is at the 3' side of a second domain.

927. The oligonucleotide of any one of the preceding Embodiments, wherein in the second domain the first subdomain is at the 5' side of the second subdomain, and the third subdomain is at the 3' side of the second subdomain.

928. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises a 5'-$N_1N_0N_{-1}$-3', wherein each of N_{-1}, N_0, and N_1 is independently a nucleoside.

929. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 5'-$N_2N_1N_0N_{-1}N_{-2}$-3' wherein each of N_2, N_1, N_0, N_{-1}, and N_{-2} is independently a nucleoside.

930. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 5'-$N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}$-3' wherein each of N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, and N_{-3} is independently a nucleoside.

931. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 5'-$N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}$-3' wherein each of N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, and N_{-4} is independently a nucleoside.

932. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 5'-$N_5N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}$-3' wherein each of N_5, N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, and N_{-5} is independently a nucleoside.

933. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 5'-$N_6N_5N_4N_3N_2N_1N_0N_{-1}N_{-2}N_{-3}N_{-4}N_{-5}N_{-6}$-3' wherein each of N_6, N_5, N_4, N_3, N_2, N_1, N_0, N_{-1}, N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a nucleoside.

934. The oligonucleotide of any one of the preceding Embodiments, wherein the second subdomain comprises a 5'-$N_1N_0N_{-1}$-3', wherein each of N_{-1}, N_0, and N_1 is independently a nucleoside.

935. An oligonucleotide comprising a 5'-$N_1N_0N_{-1}$-3' as described in the present disclosure.

936. The oligonucleotide of any one of the preceding Embodiments, wherein when the oligonucleotide is

aligned with a target nucleic acid, N_0 is opposite to a target adenosine.

937. The oligonucleotide of any one of the preceding Embodiments, wherein each of N_{-1}, N_0, and N_1 independently has a 2'-F modified sugar, a natural RNA sugar, or a sugar having no 2'-substituent replacing 2'−OH of a natural RNA sugar.

938. The oligonucleotide of any one of the preceding Embodiments, wherein each of N_{-1}, N_0, and N_1 independently has a 2'-F modified sugar, a natural RNA sugar, or a sugar having no 2'-substituents.

939. The oligonucleotide of any one of the preceding Embodiments, wherein each of N_{-1}, N_0, and N_1 independently has a 2'-F modified sugar, a natural RNA sugar, or a natural DNA sugar.

940. The oligonucleotide of any one of the preceding Embodiments, wherein no more than one of N_{-1}, N_0, and N_1 has a 2'-F modified sugar.

941. The oligonucleotide of any one of the preceding Embodiments, wherein no more than one of N_{-1}, N_0, and N_1 has a natural RNA sugar.

942. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_1 is a 2'-F modified sugar.

943. The oligonucleotide of any one of Embodiments 1-941, wherein the sugar of N_0 is a sugar comprising no substituent at a position corresponding to 2'−OH of a natural RNA sugar.

944. The oligonucleotide of any one of Embodiments 1-941, wherein the sugar of N_0 is a sugar comprising no 2'-substituent.

945. The oligonucleotide of any one of Embodiments 1-941, wherein the sugar of N_1 is a natural DNA sugar.

946. The oligonucleotide of any one of Embodiments 1-941, wherein the sugar of N_1 is a natural RNA sugar.

947. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_0 is a modified sugar.

948. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_0 is a 2'-F modified sugar.

949. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar comprising no substituent at a position corresponding to 2'−OH of a natural RNA sugar.

950. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar comprising no 2'-substituent.

951. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is a 5'-modified sugar.

952. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is a 5'-Me modified sugar.

953. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is a non-cyclic sugar.

954. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is sm01.

955. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is sm15.

956. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a sugar is a substituted natural DNA sugar one of whose 2'-H is substituted with −OH or −F and the other 2'-H is not substituted.

957. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a natural DNA sugar.

958. The oligonucleotide of any one of Embodiments 1-946, wherein the sugar of N_0 is a natural RNA sugar.

959. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is C.

960. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is hypoxanthine.

961. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is T.

962. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is A.

963. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is G.

964. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is U.

965. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b001U.

966. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b002U.

967. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b003U.

968. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b004U.

969. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b005U.

970. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b006U.

971. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b007U.

972. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b008U.

973. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b009U.

974. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b011U.

975. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b012U.

976. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b013U.

977. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b001A.

978. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b002A.

979. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b003A.

980. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b001G.

981. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b002G.

982. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b001C.

983. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b002C.

984. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b003C.

985. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b004C.

986. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b005C.

987. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b006C.

988. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b007C.

989. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b008C.

990. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b009C.

991. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b002I.

992. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b003I.

993. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b004I.

994. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is b014I.

995. The oligonucleotide of any one of Embodiments 1-958, wherein the nucleobase of N_0 is zndp.

996. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dC.

997. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fU.

998. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dU.

999. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fA.

1000. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dA.

1001. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fT.

1002. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dT.

1003. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fC.

1004. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fG.

1005. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dG.

1006. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is dI.

1007. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is fI.

1008. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is aC.

1009. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is m5dC.

1010. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is 5MRm5dC.

1011. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is 5MSm5dC.

1012. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b001G.

1013. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b002G.

1014. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b001C.

1015. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b002C.

1016. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b003C.

1017. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b003mC.

1018. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b004C.

1019. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b005C.

1020. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b006C.

1021. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b007C.

1022. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b008C.

1023. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b009C.

1024. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b001A.

1025. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b002A.

1026. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b003A.

1027. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b001U.

1028. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b002U.

1029. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b003U.

1030. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b004U.

1031. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b005U.

1032. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b006U.

1033. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b007U.

1034. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b008U.

1035. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b009U.

1036. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b010U.

1037. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b011U.

1038. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b012U.

1039. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b013U.

1040. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b002I.

1041. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b003I.

1042. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b004I.

1043. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b014I.

1044. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Asm01.

1045. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Gsm01.

1046. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Tsm01.

1047. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is 5MSfC.

1048. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Usm04.

1049. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is 5MRdT.

1050. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm04.

1051. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm11.

1052. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Gsm11.

1053. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Tsm11.

1054. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b009Csm11.

1055. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b009Csm12.

1056. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Gsm12.

1057. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Tsm12.

1058. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm12.

1059. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is rCsm13.

1060. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is rCsm14.

1061. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm15.

1062. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm16.

1063. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm17.

1064. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is abasic.

1065. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is L010.

1066. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is L034.

1067. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Csm15.

1068. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is Tsm18.

1069. The oligonucleotide of any one of Embodiments 1-946, wherein N_0 is b001rA.

1070. The oligonucleotide of any one of the preceding Embodiments, wherein nucleobase of N_1 is A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp.

1071. The oligonucleotide of any one of the preceding Embodiments, wherein nucleobase of N_1 is a modified nucleobase.

1072. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_1 is a 2'-F modified sugar.

1073. The oligonucleotide of any one of Embodiments 1-1070, wherein the sugar of N_1 is a sugar comprising no substituent at a position corresponding to 2'−OH of a natural RNA sugar.

1074. The oligonucleotide of any one of Embodiments 1-1070, wherein the sugar of N_1 is a sugar comprising no 2'-substituent.

1075. The oligonucleotide of any one of Embodiments 1-1070, wherein the sugar of N_1 is a natural DNA sugar.

1076. The oligonucleotide of any one of Embodiments 1-1070, wherein the sugar of N_1 is a natural RNA sugar.

1077. The oligonucleotide of any one of Embodiments 1-1070, where N_1 is dA, dT, dC, dG, dU, fA, fT, fC, fG or fU.

1078. The oligonucleotide of any one of Embodiments 1-1076, where the nucleobase of N_1 is A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp.

1079. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b001A.

1080. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b002A.

1081. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b003A.

1082. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b001C.

1083. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b004C.

1084. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b007C.

1085. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b008C.

1086. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b008U.

1087. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b010U.

1088. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b011U.

1089. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b012U.

1090. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Csm11.

1091. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Csm12.

1092. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Csm17.

1093. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b009Csm11.

1094. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is b009Csm12.

1095. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Gsm01.

1096. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Gsm11.

1097. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Gsm12.

1098. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Tsm01.

1099. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Tsm11.

1100. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Tsm12.

1101. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is Tsm18.

1102. The oligonucleotide of any one of Embodiments 1-1070, wherein N_1 is L010.

1103. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_{-1} is a modified sugar.

1104. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of N_{-1} is a 2'-F modified sugar.

1105. The oligonucleotide of any one of Embodiments 1-1102, wherein the sugar of N_{-1} is a sugar comprising no substituent at a position corresponding to 2'−OH of a natural RNA sugar.

1106. The oligonucleotide of any one of Embodiments 1-1102, wherein the sugar of N_{-1} is a sugar comprising no 2'-substituent.

1107. The oligonucleotide of any one of Embodiments 1-1102, wherein the sugar of N_{-1} is a natural DNA sugar.

1108. The oligonucleotide of any one of Embodiments 1-1102, wherein the sugar of N_{-1} is a natural RNA sugar.

1109. The oligonucleotide of any one of the preceding Embodiments, wherein N_1 and N_{-1} are both complementary to their corresponding nucleosides when the oligonucleotide is aligned with a target nucleic acid.

1110. The oligonucleotide of any one of the preceding Embodiments, wherein at least one of N_1 and N_{-1} is independently produces a mismatch or a wobble base pairing when the oligonucleotide is aligned with a target nucleic acid.

1111. The oligonucleotide of Embodiment 1110, wherein the oligonucleotide provides comparable or higher editing levels of a target adenosine compared to a reference oligonucleotide, wherein the reference oligonucleotide is otherwise identical but has N_1 and N_{-1} that are complementary to their corresponding nucleosides when the reference oligonucleotide is aligned with the target nucleic acid, wherein the target adenosine is opposite to N_0 when the oligonucleotide is aligned with the target nucleic acid.

1112. The oligonucleotide of any one of the preceding Embodiments, wherein the nucleobase of N_{-1} is A, T, C, G, U, hypoxanthine, b001U, b002U, b003U, b004U, b005U, b006U, b007U, b008U, b009U, b011U, b012U, b013U, b001A, b002A, b003A, b001G, b002G, b001C, b002C, b003C, b004C, b005C, b006C, b007C, b008C, b009C, b002I, b003I, b004I, b014I, or zdnp.

1113. The oligonucleotide of any one of the preceding Embodiments, wherein the nucleobase of N_{-1} is a modified nucleobase.

1114. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is hypoxanthine.

1115. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is C.

1116. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is T.

1117. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is A.

1118. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is G.

1119. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is U.

1120. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b001U.

1121. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b002U.

1122. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b003U.

1123. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b004U.

1124. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b005U.

1125. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b006U.

1126. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b007U.

1127. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b008U.

1128. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b009U.

1129. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b011U.

1130. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b012U.

1131. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b013U.

1132. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b001A.

1133. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b002A.

1134. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b003A.

1135. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b001G.

1136. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b002G.

1137. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b001C.

1138. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b002C.

1139. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b003C.

1140. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b004C.

1141. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b005C.

1142. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b006C.

1143. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b007C.

1144. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b008C.

1145. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b009C.

1146. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b002I.

1147. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b003I.

1148. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b004I.

1149. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is b014I.

1150. The oligonucleotide of any one of Embodiments 1-1111, wherein the nucleobase of N_{-1} is zndp.

1151. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dC.

1152. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fU.

1153. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dU.

1154. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fA.

1155. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dA.

1156. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fT.

1157. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dT.

1158. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fC.

1159. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fG.

1160. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dG.

1161. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is dI.

1162. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is fI.

1163. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is aC.

1164. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is m5dC.

1165. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is 5MRm5dC.

1166. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is 5MSm5dC.

1167. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b001G.

1168. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b002G.

1169. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b001C.

1170. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b002C.

1171. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b003C.

1172. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b003mC.

1173. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b004C.

1174. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b005C.

1175. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b006C.

1176. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b007C.

1177. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b008C.

1178. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b009C.

1179. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b001A.

1180. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b002A.

1181. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b003A.

1182. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b001U.

1183. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b002U.

1184. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b003U.

1185. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b004U.

1186. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b005U.

1187. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b006U.

1188. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b007U.

1189. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b008U.

1190. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b009U.

1191. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b010U.

1192. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b011U.

1193. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b012U.

1194. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b013U.

1195. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b002I.

1196. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b003I.

1197. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b004I.

1198. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b014I.

1199. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Asm01.

1200. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Gsm01.

1201. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is 5MSfC.

1202. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Usm04.

1203. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is 5MRdT.

1204. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm04.

1205. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm11.

1206. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Gsm11.

1207. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Tsm11.

1208. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b009Csm11.

1209. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b009Csm12.

1210. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Gsm12.

1211. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Tsm12.

1212. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm12.

1213. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is rCsm13.

1214. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is rCsm14.

1215. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm15.

1216. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm16.

1217. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm17.

1218. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is abasic.

1219. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is L010.

1220. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is L034.

1221. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Csm15.

1222. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is Tsm18.

1223. The oligonucleotide of any one of Embodiments 1-1111, wherein N_{-1} is b001rA.

1224. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_0 and N_1 is a phosphorothioate internucleotidic linkage.

1225. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_0 and N_1 is a *S*p phosphorothioate internucleotidic linkage.

1226. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_0 and N_{-1} is a phosphorothioate internucleotidic linkage.

1227. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_0 and N_{-1} is a *S*p phosphorothioate internucleotidic linkage.

1228. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_2 is a modified sugar.

1229. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_2 is a 2'-F modified sugar.

1230. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_1 and N_2 is a phosphorothioate internucleotidic linkage.

1231. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_1 and N_2 is a *S*p phosphorothioate internucleotidic linkage.

1232. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_3 is a modified sugar.

1233. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_3 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1234. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_3 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1235. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_3 is a 2'-OMe modified sugar.

1236. The oligonucleotide of Embodiment 1233, wherein sugar of N_3 is a 2'-MOE modified sugar.

1237. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_2 and N_3 is natural phosphate linkage.

1238. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_4 is a modified sugar.

1239. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_4 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1240. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_4 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1241. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_4 is a 2'-OMe modified sugar.

1242. The oligonucleotide of Embodiment 1239, wherein sugar of N_4 is a 2'-MOE modified sugar.

1243. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_3 and N_4 is a natural phosphate linkage.

1244. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_5 is a modified sugar.

1245. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_5 is a 2'-F modified sugar.

1246. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_4 and N_5 is a non-negatively charged internucleotidic linkage.

1247. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_4 and N_5 is a phosphoryl guanidine internucleotidic linkage.

1248. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_4 and N_5 is n001.

1249. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_4 and N_5 is *R*p n001.

1250. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_6 is a modified sugar.

1251. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_6 is a 2'-F modified sugar.

1252. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_5 and N_6 is a phosphorothioate internucleotidic linkage internucleotidic linkage.

1253. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_5 and N_6 is a *S*p phosphorothioate internucleotidic linkage internucleotidic linkage.

1254. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-2} is a modified sugar.

1255. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-2} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1256. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-2} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1257. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-2} is a 2'-OMe modified sugar.

1258. The oligonucleotide of Embodiment 1255, wherein sugar of N_{-2} is a 2'-MOE modified sugar.

1259. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is a non-negatively charged internucleotidic linkage.

1260. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is a phosphoryl guanidine internucleotidic linkage.

1261. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is n004, n008, n025, n026.

1262. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is *R*p n004, n008, n025, n026.

1263. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is *S*p n004, n008, n025, n026.

1264. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is n001.

1265. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is *R*p n001.

1266. The oligonucleotide of Embodiment 1264, wherein the internucleotidic linkage between N_{-1} and N_{-2} is *S*p n001.

1267. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-3} is a modified sugar.

1268. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-3} is a 2'-F modified sugar.

1269. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage

between N_{-2} and N_{-3} is a natural phosphate linkage.

1270. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-4} is a modified sugar.

1271. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-4} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1272. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-4} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1273. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-4} is a 2'-OMe modified sugar.

1274. The oligonucleotide of Embodiment 1271, wherein sugar of N_{-4} is a 2'-MOE modified sugar.

1275. The oligonucleotide of any one of the preceding Embodiments, wherein the linkage between N_{-3} and N_{-4} is a phosphorothioate internucleotidic linkage.

1276. The oligonucleotide of any one of the preceding Embodiments, wherein the linkage between N_{-3} and N_{-4} is a *Sp* phosphorothioate internucleotidic linkage.

1277. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-5} is a modified sugar.

1278. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-5} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1279. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-5} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1280. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-5} is a 2'-OMe modified sugar.

1281. The oligonucleotide of Embodiment 1278, wherein sugar of N_{-5} is a 2'-MOE modified sugar.

1282. The oligonucleotide of any one of the preceding Embodiments, wherein the linkage between N_{-4} and N_{-5} is a phosphorothioate internucleotidic linkage.

1283. The oligonucleotide of any one of the preceding Embodiments, wherein the linkage between N_{-4} and N_{-5} is a *Sp* phosphorothioate internucleotidic linkage.

1284. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-6} is a modified sugar.

1285. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-6} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1286. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-6} is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1287. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_{-6} is a 2'-OMe modified sugar.

1288. The oligonucleotide of Embodiment 1278, wherein sugar of N_{-6} is a 2'-MOE modified sugar.

1289. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-5} and N_{-6} is a non-negatively charged internucleotidic linkage.

1290. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-5} and N_{-6} is a phosphoryl guanidine internucleotidic linkage.

1291. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-5} and N_{-6} is n001.

1292. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-5} and N_{-6} is *R*p n001.

1293. The oligonucleotide of any one of the preceding Embodiments, wherein about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80% of its sugars are each independently a 2'-F modified sugar.

1294. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% of its sugars are each independently a 2'-F modified sugar.

1295. The oligonucleotide of any one of the preceding Embodiments, wherein about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80% of its sugars are each independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1296. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% of its sugars are each independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1297. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% of its sugars are each independently a 2'-OMe or 2'-MOE modified sugar.

1298. The oligonucleotide of any one of the preceding Embodiments, wherein about 20%-80%, 30-70%, 30%-60%, 30%-50%, 40%-60%, 20%, 30%, 40%, 50%, 60%, 70% or 80% of its sugars in a first domain are each independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1299. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% of its sugars in a first domain are each independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1300. The oligonucleotide of any one of the preceding Embodiments, wherein about 30%-60% of its sugars in a first domain are each independently a 2'-OMe or 2'-MOE modified sugar.

1301. The oligonucleotide of any one of the preceding Embodiments, wherein the 3'-end nucleoside of a first domain is N_2.

1302. The oligonucleotide of any one of the preceding Embodiments, wherein the 5'-end nucleoside of a first domain is the 5'-end nucleoside of the oligonucleotide.

1303. The oligonucleotide of any one of the preceding Embodiments, wherein about or at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., are independently bonded to a natural phosphate linkage.

1304. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1305. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1306. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-OMe modified sugar.

1307. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_{-2}, N_{-3}, N_{-4}, N_{-5}, and N_{-6} is independently a 2'-MOE modified sugar.

1308. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_2, N_3, N_4, N_5, N_6, N_7, and N_8 is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1309. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_2, N_3, N_4, N_5, N_6, N_7, and N_8 is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1310. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_2, N_3, N_4, N_5, N_6, N_7, and N_8 is independently a 2'-OMe modified sugar.

1311. The oligonucleotide of any one of the preceding Embodiments, wherein each of one or more sugars of N_2, N_3, N_4, N_5, N_6, N_7, and N_8 is independently a 2'-MOE modified sugar.

1312. The oligonucleotide of any one of the preceding Embodiments, wherein about or at least about 50% 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic in an oligonucleotide or a portion thereof, e.g., a first domain, a second domain, etc., are independently bonded to a natural phosphate linkage.

1313. The oligonucleotide of any one of the preceding Embodiments, wherein at least 60%, 70%, 80% or 90% or all natural phosphate linkages each independently bond to at least one modified sugar which is 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic or a bicyclic sugar.

1314. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently a natural phosphate linkage.

1315. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in a first domain are independently a natural phosphate linkage.

1316. The oligonucleotide of any one of the preceding Embodiments, wherein one or more internucleotidic linkages at one or more of positions +3 (between $N_{+4}N_{+3}$), +4, +6, +8, +9, +12, +14, +15, +17, and +18 are

independently a natural phosphate linkage.

1317. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, 30%-70%, 40-70%, 40%-65%, 40%-60%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or 65% of all internucleotidic linkages in an oligonucleotide are independently a phosphorothioate internucleotidic linkage.

1318. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 15-40%, 20-30%, 25-30%, 30%-70%, 40-70%, 40%-65%, 40%-60%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or 65% of all internucleotidic linkages in a first domain are independently a phosphorothioate internucleotidic linkage.

1319. The oligonucleotide of any one of the preceding Embodiments, wherein one or more internucleotidic linkages at one or more of positions +1 (between $N_{+1}N_0$), +2, +5, +6, +7, +8, +11, +14, +15, +16, +17, +19, +20, +21, and +22 are independently a phosphorothioate internucleotidic linkage.

1320. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently a non-negatively charged internucleotidic linkage.

1321. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in a first domain are independently a non-negatively charged internucleotidic linkage.

1322. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently a phosphoryl guanidine internucleotidic linkage.

1323. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in a first domain are independently a phosphoryl guanidine internucleotidic linkage.

1324. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%,

15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in an oligonucleotide are independently n001.

1325. The oligonucleotide of any one of the preceding Embodiments, wherein about 5%-90%, about 10-80%, about 10-75%, about 10-70%, 10%-60%, 10-50%, 10-40%, 10-30%, 10%-20%, 10-15%, 15-40%, 15%-35%, 15%-30%, 15-25%, 15-20%, or about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, of all internucleotidic linkages in a first domain are independently n001.

1326. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all of positions +5 (between $N_{+5}N_{+4}$), +10, +13 or +23 are independently a non-negatively charged internucleotidic linkage.

1327. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all of positions +5 (between $N_{+5}N_{+4}$), +10, +13 or +23 are independently a phosphoryl guanidine internucleotidic linkage.

1328. The oligonucleotide of any one of the preceding Embodiments, wherein one or more or all of positions +5 (between $N_{+5}N_{+4}$), +10, +13 or +23 are independently n001.

1329. The oligonucleotide of any one of the preceding Embodiments, wherein sugar of N_4 is a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1330. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_3 and N_4 is natural phosphate linkage.

1331. The oligonucleotide of any one of the preceding Embodiments, wherein there are 5 or more nucleosides at the 3' side of N_0.

1332. The oligonucleotide of any one of the preceding Embodiments, wherein there are 6 or more nucleosides at the 3' side of N_0.

1333. The oligonucleotide of any one of the preceding Embodiments, wherein there are 7 or more nucleosides at the 3' side of N_0.

1334. The oligonucleotide of any one of the preceding Embodiments, wherein there are 8 or more nucleosides at the 3' side of N_0.

1335. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 3 nucleosides at the 3' side of N_0.

1336. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 4 nucleosides at the 3' side of N_0.

1337. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 5 nucleosides at the 3' side of N_0.

1338. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 6 nucleosides at the 3' side of N_0.

1339. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 7 nucleosides at the 3' side of N_0.

1340. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 8 nucleosides at the 3' side of N_0.

1341. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 9 nucleosides at the 3' side of N_0.

1342. The oligonucleotide of any one of Embodiments 1-1330, wherein there are 10 nucleosides at the 3' side of N_0.

1343. The oligonucleotide of any one of the preceding Embodiments, wherein there are 5 or more (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more) nucleosides at the 5' side of N_0.

1344. The oligonucleotide of any one of the preceding Embodiments, wherein there are 8 or more nucleosides at the 5' side of N_0.

1345. The oligonucleotide of any one of the preceding Embodiments, wherein there are 10 or more nucleosides at the 5' side of N_0.

1346. The oligonucleotide of any one of the preceding Embodiments, wherein there are 15 or more nucleosides at the 5' side of N_0.

1347. The oligonucleotide of any one of the preceding Embodiments, wherein there are 16 or more nucleosides at the 5' side of N_0.

1348. The oligonucleotide of any one of the preceding Embodiments, wherein there are 17 or more nucleosides at the 5' side of N_0.

1349. The oligonucleotide of any one of the preceding Embodiments, wherein there are 18 or more nucleosides at the 5' side of N_0.

1350. The oligonucleotide of any one of the preceding Embodiments, wherein there are 19 or more nucleosides at the 5' side of N_0.

1351. The oligonucleotide of any one of the preceding Embodiments, wherein there are 20 or more nucleosides at the 5' side of N_0.

1352. The oligonucleotide of any one of the preceding Embodiments, wherein there are 21 or more nucleosides at the 5' side of N_0.

1353. The oligonucleotide of any one of the preceding Embodiments, wherein there are 22 or more nucleosides at the 5' side of N_0.

1354. The oligonucleotide of any one of the preceding Embodiments, wherein there are 23 or more nucleosides at the 5' side of N_0.

1355. The oligonucleotide of any one of the preceding Embodiments, wherein there are 24 or more nucleosides at the 5' side of N_0.

1356. The oligonucleotide of any one of the preceding Embodiments, wherein there are 25 or more nucleosides at the 5' side of N_0.

1357. The oligonucleotide of any one of the preceding Embodiments, wherein there are 26 or more

nucleosides at the 5’ side of N_0.

1358. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 20 nucleosides at the 5’ side of N_0.

1359. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 21 nucleosides at the 5’ side of N_0.

1360. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 22 nucleosides at the 5’ side of N_0.

1361. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 23 nucleosides at the 5’ side of N_0.

1362. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 24 nucleosides at the 5’ side of N_0.

1363. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 25 nucleosides at the 5’ side of N_0.

1364. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 26 nucleosides at the 5’ side of N_0.

1365. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 27 nucleosides at the 5’ side of N_0.

1366. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 28 nucleosides at the 5’ side of N_0.

1367. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 29 nucleosides at the 5’ side of N_0.

1368. The oligonucleotide of any one of Embodiments 1-1343, wherein there are 30 nucleosides at the 5’ side of N_0.

1369. The oligonucleotide of any one of the preceding Embodiments, wherein the first 1, 2, 3, 4, or 5 sugars at the 5’-end of the oligonucleotide are each independently sugars that can increase stability.

1370. The oligonucleotide of any one of the preceding Embodiments, wherein the first 3 sugars at the 5’-end of the oligonucleotide are each independently sugars that can increase stability.

1371. The oligonucleotide of any one of the preceding Embodiments, wherein the first 4 sugars at the 5’-end of the oligonucleotide are each independently sugars that can increase stability.

1372. The oligonucleotide of any one of the preceding Embodiments, wherein the first 5 sugars at the 5’-end of the oligonucleotide are each independently sugars that can increase stability.

1373. The oligonucleotide of any one of the preceding Embodiments, wherein the first 1, 2, 3, 4, or 5 sugars at the 5’-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2’-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1374. The oligonucleotide of any one of the preceding Embodiments, wherein the first 3 sugars at the 5’-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2’-OR modified sugar,

wherein R is optionally substituted C_{1-6} aliphatic.

1375. The oligonucleotide of any one of the preceding Embodiments, wherein the first 4 sugars at the 5'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1376. The oligonucleotide of any one of the preceding Embodiments, wherein the first 5 sugars at the 5'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1377. The oligonucleotide of any one of the preceding Embodiments, wherein the first 3 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1378. The oligonucleotide of any one of the preceding Embodiments, wherein the first 4 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1379. The oligonucleotide of any one of the preceding Embodiments, wherein the first 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1380. The oligonucleotide of any one of the preceding Embodiments, wherein the first 1, 2, 3, 4, or 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OMe or 2'-MOE modified sugar.

1381. The oligonucleotide of any one of the preceding Embodiments, wherein the first 1, 2, 3, 4, or 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1382. The oligonucleotide of any one of the preceding Embodiments, wherein the first 3 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1383. The oligonucleotide of any one of the preceding Embodiments, wherein the first 4 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1384. The oligonucleotide of any one of the preceding Embodiments, wherein the first 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1385. The oligonucleotide of any one of Embodiments 1-1380, wherein the first 1, 2, 3, 4, or 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-MOE modified sugar.

1386. The oligonucleotide of any one of Embodiments 1-1380, wherein the first 3 sugars at the 5'-end of the oligonucleotide are each independently a 2'-MOE modified sugar.

1387. The oligonucleotide of any one of Embodiments 1-1380, wherein the first 4 sugars at the 5'-end of the oligonucleotide are each independently a 2'-MOE modified sugar.

1388. The oligonucleotide of any one of Embodiments 1-1380, wherein the first 5 sugars at the 5'-end of the oligonucleotide are each independently a 2'-MOE modified sugar.

1389. The oligonucleotide of any one of the preceding Embodiments, wherein the last 1, 2, 3, 4, or 5 sugars at the 3'-end of the oligonucleotide are each independently sugars that can increase stability.

1390. The oligonucleotide of any one of the preceding Embodiments, wherein the last 3 sugars at the 3'-end of the oligonucleotide are each independently sugars that can increase stability.

1391. The oligonucleotide of any one of the preceding Embodiments, wherein the last 4 sugars at the 3'-end of the oligonucleotide are each independently sugars that can increase stability.

1392. The oligonucleotide of any one of the preceding Embodiments, wherein the last 5 sugars at the 3'-end of the oligonucleotide are each independently sugars that can increase stability.

1393. The oligonucleotide of any one of the preceding Embodiments, wherein the last 1, 2, 3, 4, or 5 sugars at the 3'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1394. The oligonucleotide of any one of the preceding Embodiments, wherein the last 3 sugars at the 3'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1395. The oligonucleotide of any one of the preceding Embodiments, wherein the last 4 sugars at the 3'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1396. The oligonucleotide of any one of the preceding Embodiments, wherein the last 5 sugars at the 3'-end of the oligonucleotide are each independently selected from a bicyclic sugar and a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1397. The oligonucleotide of any one of the preceding Embodiments, wherein the last 3 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1398. The oligonucleotide of any one of the preceding Embodiments, wherein the last 4 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1399. The oligonucleotide of any one of the preceding Embodiments, wherein the last 5 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1400. The oligonucleotide of any one of the preceding Embodiments, wherein the last 1, 2, 3, 4, or 5 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OMe or 2'-MOE modified sugar.

1401. The oligonucleotide of any one of the preceding Embodiments, wherein the last 1, 2, 3, 4, or 5 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1402. The oligonucleotide of any one of the preceding Embodiments, wherein the last 3 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1403. The oligonucleotide of any one of the preceding Embodiments, wherein the last 4 sugars at the 3'-end of the oligonucleotide are each independently a 2'-OMe modified sugar.

1404. The oligonucleotide of any one of the preceding Embodiments, wherein the last 5 sugars at the 3'-

end of the oligonucleotide are each independently a 2’-OMe modified sugar.

1405. The oligonucleotide of any one of Embodiments 1-1400, wherein the last 1, 2, 3, 4, or 5 sugars at the 3’-end of the oligonucleotide are each independently a 2’-MOE modified sugar.

1406. The oligonucleotide of any one of Embodiments 1-1400, wherein the last 3 sugars at the 3’-end of the oligonucleotide are each independently a 2’-MOE modified sugar.

1407. The oligonucleotide of any one of Embodiments 1-1400, wherein the last 4 sugars at the 3’-end of the oligonucleotide are each independently a 2’-MOE modified sugar.

1408. The oligonucleotide of any one of Embodiments 1-1400, wherein the last 5 sugars at the 3’-end of the oligonucleotide are each independently a 2’-MOE modified sugar.

1409. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end of an oligonucleotide is a non-negatively charged internucleotidic linkage.

1410. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end of an oligonucleotide is a neutral internucleotidic linkage.

1411. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end of an oligonucleotide is phosphoryl guanidine internucleotidic linkage.

1412. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end of an oligonucleotide is n004, n008, n025, n026.

1413. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end of an oligonucleotide is n001.

1414. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 5’-end is chirally controlled and is *R*p.

1415. The oligonucleotide of any one of Embodiments 1-1413, wherein the first internucleotidic linkage from the 5’-end is chirally controlled and is *S*p.

1416. The oligonucleotide of any one of the preceding Embodiments, wherein both internucleotidic linkages bonded to the 3rd nucleosides from the 5’-end are each independently a phosphorothioate internucleotidic linkages.

1417. The oligonucleotide of any one of the preceding Embodiments, wherein both internucleotidic linkages bonded to the 4th nucleosides from the 5’-end are each independently a phosphorothioate internucleotidic linkages.

1418. The oligonucleotide of any one of the preceding Embodiments, wherein both internucleotidic linkages bonded to the 5th nucleosides from the 5’-end are each independently a phosphorothioate internucleotidic linkages.

1419. The oligonucleotide of any one of Embodiments 1416-1418, wherein each phosphorothioate internucleotidic linkage is chirally controlled.

1420. The oligonucleotide of Embodiment 1419, wherein each phosphorothioate internucleotidic linkage is *S*p.

1421. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end of an oligonucleotide is a non-negatively charged internucleotidic linkage.

1422. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end of an oligonucleotide is a neutral internucleotidic linkage.

1423. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end of an oligonucleotide is phosphoryl guanidine internucleotidic linkage.

1424. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end of an oligonucleotide is n004, n008, n025, n026.

1425. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end of an oligonucleotide is n001.

1426. The oligonucleotide of any one of the preceding Embodiments, wherein the first internucleotidic linkage from the 3’-end is chirally controlled and is *R*p.

1427. The oligonucleotide of any one of Embodiments 1-1426, wherein the first internucleotidic linkage from the 3’-end is chirally controlled and is *S*p.

1428. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside opposite to a target adenosine (position 0, such a nucleoside: N_0) is a natural DNA sugar.

1429. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position +1 (the nucleoside to the immediate 5’-side of N_0; i.e., N_{+1} of 5’-…$N_{+1}N_0$…-3’) is a natural DNA sugar.

1430. The oligonucleotide of any one of Embodiments 1-1428, wherein the sugar of the nucleoside at position +1 (the nucleoside to the immediate 5’-side of N_0; i.e., N_{+1} of 5’-…$N_{+1}N_0$…-3’) is a 2’-F modified sugar.

1431. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position +2 (N_{+2} of 5’-… $N_{+2}N_{+1}N_0$…-3’) is a 2’-F modified sugar.

1432. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position -1 (N_{-1} of 5’-… $N_{+2}N_{+1}N_0N_{-1}$…-3’) is a natural DNA sugar.

1433. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5’-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3’) is a sugar that can increase stability.

1434. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5’-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3’) is a bicyclic sugar or a 2’-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1435. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5’-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3’) is a bicyclic sugar.

1436. The oligonucleotide of any one of Embodiments 1-1434, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5’-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3’) is a 2’-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1437. The oligonucleotide of any one of Embodiments 1-1434, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5'-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3') is a 2'-OMe modified sugar.

1438. The oligonucleotide of any one of Embodiments 1-1434, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5'-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3') is a 2'-MOE modified sugar.

1439. The oligonucleotide of any one of Embodiments 1-1434, wherein the sugar of the nucleoside at position -2 (N_{-2} of 5'-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}$…-3') is a 2'-MOE modified sugar.

1440. The oligonucleotide of any one of the preceding Embodiments, wherein the sugar of the nucleoside at position -3 (N_{-3} of 5'-… $N_{+2}N_{+1}N_0N_{-1}N_{-2}N_{-3}$…-3') is a 2'-F modified sugar.

1441. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a sugar that can increase stability.

1442. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a bicyclic sugar or a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1443. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is a bicyclic sugar.

1444. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1445. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is a 2'-OMe modified sugar.

1446. The oligonucleotide of any one of the preceding Embodiments, wherein a sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is a 2'-MOE modified sugar.

1447. The oligonucleotide of any one of Embodiments 1-1442, wherein each sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a 2'-OR modified sugar, wherein R is optionally substituted C_{1-6} aliphatic.

1448. The oligonucleotide of any one of Embodiments 1-1442, wherein each sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a 2'-OMe modified sugar.

1449. The oligonucleotide of any one of Embodiments 1-1442, wherein each sugar of a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a 2'-MOE modified sugar.

1450. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage bonded to N_{+1} or N_0 is independently a phosphorothioate internucleotidic linkage.

1451. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage bonded to N_{+1} or N_0 is independently a *Sp* phosphorothioate internucleotidic linkage.

1452. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is a non-negatively charged internucleotidic linkage.

1453. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is a neutral internucleotidic linkage.

1454. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is phosphoryl guanidine internucleotidic linkage.

1455. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is n004, n008, n025, n026.

1456. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is n001.

1457. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-1} and N_{-2} is chirally controlled and is *R*p.

1458. The oligonucleotide of any one of Embodiments 1-1456, wherein the internucleotidic linkage between N_{-1} and N_{-2} is chirally controlled and is *S*p.

1459. The oligonucleotide of any one of the preceding Embodiments, wherein the internucleotidic linkage between N_{-2} and N_{-3} is a natural phosphate linkage.

1460. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage bonded to a nucleoside after N_{-3} (e.g., N_{-4}, N_{-5}, N_{-6}, etc.) is independently a phosphorothioate internucleotidic linkage except the first internucleotidic linkage from the 3'-end.

1461. The oligonucleotide of Embodiment 1460, wherein the phosphorothioate internucleotidic linkage is chirally controlled and is *S*p.

1462. The oligonucleotide of any one of the preceding Embodiments, wherein a bicyclic sugar is a LNA sugar or a cEt sugar.

1463. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) natural phosphate linkages.

1464. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises no more than 5 (e.g., 1, 2, 3, 4, or 5) natural phosphate linkages.

1465. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises no more than 10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) n001.

1466. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide comprises no more than 10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) phosphoryl guanidine internucleotidic linkages.

1467. An oligonucleotide comprising a duplexing region and a targeting region, wherein a targeting region is or comprises a second region of any one of the preceding Embodiments.

1468. An oligonucleotide comprising a duplexing region and a targeting region, wherein a targeting region is or comprises 5'-$N_1N_0N_{-1}$-3' of any one of the preceding Embodiments.

1469. The oligonucleotide of any one of Embodiments 1467-1468, wherein a duplexing region is capable of forming a duplex with a nucleic acid (a duplexing nucleic acid).

1470. The oligonucleotide of any one of Embodiments 1467-1469, wherein a targeting region is capable of forming a duplex with a target nucleic acid comprising a target adenosine.

1471. The oligonucleotide of any one of Embodiments 1467-1470, wherein a duplexing nucleic acid is not

a target nucleic acid.

1472. The oligonucleotide of any one of Embodiments 1467-1470, wherein the oligonucleotide is an oligonucleotide of any one of Embodiments 1-1466.

1473. The oligonucleotide of any one of Embodiments 1467-1472, wherein the length of a targeting region is about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleosides.

1474. The oligonucleotide of any one of Embodiments 1467-1473, wherein the length of a duplexing region is about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleosides.

1475. The oligonucleotide of any one of Embodiments 1467-1474, wherein the length of a duplexing oligonucleotide is about or at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleosides.

1476. The oligonucleotide of any one of Embodiments 1467-1475, wherein a duplexing oligonucleotide comprises a step loop.

1477. The oligonucleotide of any one of Embodiments 1467-1476, wherein the oligonucleotide comprises one or more modified sugars, one or more modified internucleotidic linkages, and one or more natural phosphate linkages.

1478. The oligonucleotide of any one of Embodiments 1467-1477, wherein the oligonucleotide is not chirally controlled.

1479. The oligonucleotide of any one of Embodiments 1467-1478, wherein the duplexing oligonucleotide comprises one or more modified sugars and one or more modified internucleotidic linkages.

1480. The oligonucleotide of any one of Embodiments 1467-1479, wherein the majority of or all sugars in the duplexing oligonucleotide are modified sugars.

1481. The oligonucleotide of any one of Embodiments 1467-1479, wherein the majority of or all sugars in the duplexing oligonucleotide are 2'-F modified sugars.

1482. The oligonucleotide of any one of Embodiments 1467-1479, wherein the majority of or all sugars in the duplexing oligonucleotide are 2'-OR modified sugars, wherein R is optionally substituted C_{1-6} aliphatic.

1483. The oligonucleotide of any one of Embodiments 1467-1479, wherein the majority of or all sugars in the duplexing oligonucleotide are 2'-OMe modified sugars

1484. The oligonucleotide of any one of Embodiments 1467-1483, wherein the majority of or all internucleotidic linkages in the duplexing oligonucleotide are modified.

1485. The oligonucleotide of any one of Embodiments 1467-1484, wherein the majority of or all internucleotidic linkages in the duplexing oligonucleotide are phosphorothioate internucleotidic linkages.

1486. The oligonucleotide of any one of Embodiments 1467-1485, wherein the duplexing oligonucleotide is chirally controlled.

1487. The oligonucleotide of any one of Embodiments 1467-1486, wherein the majority of or all

internucleotidic linkages in the duplexing oligonucleotide are *S*p phosphorothioate internucleotidic linkages.

1488. The oligonucleotide of any one of Embodiments 1467-1487, wherein the oligonucleotide and its duplexing oligonucleotide are administered as a duplex.

1489. The oligonucleotide of any one of Embodiments 1467-1487, wherein the oligonucleotide and its duplexing oligonucleotide are administered separately.

1490. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar is independently selected from a natural DNA sugar, a natural RNA sugar, a 2'-F modified sugar, and a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

1491. The oligonucleotide of any one of the preceding Embodiments, wherein each sugar is independently selected from a natural DNA sugar, a natural RNA sugar, a 2'-F modified sugar, and a 2'-OMe or a 2'-MOE modified sugar.

1492. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage is independently selected from a natural phosphate linkage, a non-negatively charged internucleotidic linkage, and a phosphorothioate internucleotidic linkage.

1493. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage is independently selected from a natural phosphate linkage, a neutral internucleotidic linkage, and a phosphorothioate internucleotidic linkage.

1494. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage is independently selected from a natural phosphate linkage, a phosphoryl guanidine internucleotidic linkage, and a phosphorothioate internucleotidic linkage.

1495. The oligonucleotide of any one of the preceding Embodiments, wherein each internucleotidic linkage is independently selected from a natural phosphate linkage, n001, and a phosphorothioate internucleotidic linkage.

1496. An oligonucleotide having the structure of

Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1497. An oligonucleotide having the structure of

Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1498. An oligonucleotide having the structure of

Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1499. An oligonucleotide having the structure of

Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1500. An oligonucleotide having the structure of

Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*Sm CfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1501. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmCfC *SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1502. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC *SfC*SfU*SfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1503. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*S fC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1504. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SmGn001RfUmC*SfC *SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1505. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUmC* SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1506. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUm5C eo*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1507. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUm CmC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1508. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUm5 CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1509. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*Sm5CeoTeo*SmUn001Rm5CeofA*SfGn001 RmUm5Ceom5Ceo*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1510. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*SmUmUn001RmCfA*SfGn001RfUm5C eo*SfC*SmCmUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1511. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUm5Ce o*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU.

1512. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in a

salt form.

1513. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide is in a pharmaceutically acceptable salt form.

1514. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of one or more (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) chiral linkage phosphorus centers is independently about or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1515. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of one or more (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) chiral linkage phosphorus centers is independently about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1516. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of each phosphorothioate linkage phosphorus is independently about or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1517. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of each phosphorothioate linkage phosphorus is independently about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1518. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of each chiral linkage phosphorus centers is independently about or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1519. The oligonucleotide of any one of the preceding Embodiments, wherein diastereomeric excess of each chiral linkage phosphorus centers is independently about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

1520. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a purity of about 10%-100% (e.g., about 10%-95%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, or about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.).

1521. The oligonucleotide of any one of the preceding Embodiments, wherein the oligonucleotide has a purity of about 50%-100% (e.g., about 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, or at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.).

1522. A pharmaceutical composition which comprises or delivers an effective amount of an

oligonucleotide of any one of the preceding Embodiments or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

1523. An oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of the preceding Embodiments or an acid, base, or salt form thereof.

1524. An oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of Embodiments 1637-1662, or an acid, base, or salt form thereof.

1525. An oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

1526. The composition of Embodiment 1525, wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid with 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches which are not Watson-Crick base pairs.

1527. The composition of Embodiment 1525, wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid with 0-5 mismatches which are not Watson-Crick base pairs.

1528. The composition of Embodiment 1525, wherein the common base sequence is 100% complementary

to a base sequence of a portion of a nucleic acid across the length of the common base sequence except the nucleoside opposite to a target adenosine.

1529. The composition of Embodiment 1525, wherein the common base sequence is 100% complementary to a base sequence of a portion of a nucleic acid across the length of the common base sequence.

1530. The composition of any one of Embodiments 1523-1529, wherein the composition can edit a target A to I when contacted with a nucleic acid in a system expressing ADAR.

1531. The composition of any one of Embodiments 1523-1530, wherein the target adenosine is a G to A mutation associated with a condition, disorder or disease.

1532. The composition of any one of Embodiments 1523-1531, wherein oligonucleotides of the plurality share the same base and sugar modifications.

1533. The composition of any one of Embodiments 1523-1532, wherein oligonucleotides of the plurality share the same pattern of backbone chiral centers.

1534. The composition of any one of Embodiments 1523-1533, wherein the composition is enriched for oligonucleotides of the plurality compared to a stereorandom preparation of the oligonucleotides wherein no internucleotidic linkages are chirally controlled.

1535. The composition of any one of Embodiments 1523-1533, wherein a non-random level of all oligonucleotides in the composition that share the common base sequence and the same base and sugar modifications are oligonucleotides of the plurality.

1536. The composition of any one of Embodiments 1523-1533, wherein a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality.

1537. The composition of any one of Embodiments 1523-1536, wherein oligonucleotides of the plurality are of the same oligonucleotide or one or more pharmaceutically acceptable salts thereof.

1538. The composition of any one of Embodiments 1523-1536, wherein oligonucleotides of the plurality are one or more pharmaceutically acceptable salts of the same acid-form oligonucleotide.

1539. The composition of any one of Embodiments 1523-1536, wherein oligonucleotides of the plurality are of the same constitution.

1540. The composition of Embodiment 1539, wherein a non-random level of all oligonucleotides in the composition that share the same base sequence as oligonucleotides of the plurality are oligonucleotides of the plurality.

1541. The composition of Embodiment 1539, wherein a non-random level of all oligonucleotides in the composition that share the same constitution are oligonucleotides of the plurality.

1542. The composition of any one of Embodiments 1523-1536, wherein oligonucleotides of the plurality are of the same structure.

1543. The composition of any one of Embodiments 1523-1542, wherein oligonucleotides of the plurality are sodium salts.

1544. The composition of any one of Embodiments 1523-1543, wherein oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at 10 or more chiral internucleotidic linkages.

1545. The composition of any one of Embodiments 1523-1544, wherein oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at each phosphorothioate internucleotidic linkages.

1546. The composition of any one of Embodiments 1523-1545, wherein oligonucleotides of the plurality do not share the same linkage phosphorus stereochemistry at one or more or any non-negatively charged internucleotidic linkages.

1547. An oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of the preceding Embodiments or an acid, base, or salt form thereof.

1548. An oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of the preceding Embodiments and Embodiments 1637-1662, or an acid, base, or salt form thereof.

1549. An oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of Embodiments 1637-1662, or an acid, base, or salt form thereof.

1550. An oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence of each plurality is independently complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

1551. The composition of Embodiment , wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid with 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches which are not Watson-Crick base pairs.

1552. The composition of Embodiment 1551, wherein the common base sequence of each plurality is independently complementary to a base sequence of a portion of a nucleic acid with 0-5 mismatches which are not Watson-Crick base pairs.

1553. The composition of Embodiment 1551, wherein the common base sequence of each plurality is independently 100% complementary to a base sequence of a portion of a nucleic acid across the length of the common base sequence except the nucleoside opposite to a target adenosine.

1554. The composition of Embodiment 1551, wherein the common base sequence of each plurality is independently 100% complementary to a base sequence of a portion of a nucleic acid across the length of the common base sequence.

1555. The composition of any one of Embodiments 1547-1554, wherein each plurality of oligonucleotides can independently edit a target A to I when contacted with a nucleic acid in a system expressing ADAR.

1556. The composition of any one of Embodiments 1547-1555, wherein a target adenosine is a G to A mutation associated with a condition, disorder or disease.

1557. The composition of any one of Embodiments 1547-1556, wherein the composition comprises two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pluralities of oligonucleotides.

1558. The composition of any one of Embodiments 1547-1557, wherein common base sequences of at least two pluralities are different.

1559. The composition of any one of Embodiments 1547-1558, wherein no two pluralities of oligonucleotides share the same common base sequence.

1560. The composition of any one of Embodiments 1547-1559, wherein at least two pluralities of oligonucleotides target different adenosine.

1561. The composition of any one of Embodiments 1547-1560, wherein no two pluralities of oligonucleotides target the same adenosine.

1562. The composition of any one of Embodiments 1547-1561, wherein at least two pluralities of oligonucleotides target different transcripts.

1563. The composition of any one of Embodiments 1547-1562, wherein no two pluralities of oligonucleotides target the same transcript.

1564. The composition of any one of Embodiments 1547-1563, wherein at least two plurality of oligonucleotides target adenosine residues in transcripts from different polynucleotides.

1565. The composition of any one of Embodiments 1547-1566, wherein no two pluralities of oligonucleotides target transcripts from the same polynucleotide.

1566. The composition of any one of Embodiments 1547-1565, wherein at least two plurality of oligonucleotides target adenosine residues in transcripts from different genes.

1567. The composition of any one of Embodiments 1547-1566, wherein no two pluralities of oligonucleotides target transcripts from the same gene.

1568. The composition of any one of Embodiments 1547-1567, wherein oligonucleotides of each plurality independently share the same base and sugar modifications within the plurality.

1569. The composition of any one of Embodiments 1547-1568, wherein oligonucleotides of each plurality independently share the same pattern of backbone chiral centers within the plurality.

1570. The composition of any one of Embodiments 1547-1569, wherein for each plurality independently, the composition is enriched for oligonucleotides of that plurality compared to a stereorandom preparation of oligonucleotides of that plurality wherein no internucleotidic linkages are chirally controlled.

1571. The composition of any one of Embodiments 1547-1570, wherein for each plurality independently, a non-random level of all oligonucleotides in the composition that share the common base sequence and the same base and sugar modifications are oligonucleotides of the plurality.

1572. The composition of any one of Embodiments 1547-1570, wherein for each plurality independently, a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality.

1573. The composition of any one of Embodiments 1547-1572, wherein for each plurality independently, oligonucleotides of the plurality are of the same oligonucleotide or one or more pharmaceutically acceptable salts thereof.

1574. The composition of any one of Embodiments 1547-1573, wherein for each plurality independently, oligonucleotides of the plurality are one or more pharmaceutically acceptable salts of the same acid-form oligonucleotide.

1575. The composition of any one of Embodiments 1547-1572, wherein for each plurality independently, oligonucleotides of the plurality are of the same constitution.

1576. The composition of Embodiment 1575, wherein for each plurality independently, a non-random level of all oligonucleotides in the composition that share the same base sequence as oligonucleotides of the plurality are oligonucleotides of the plurality.

1577. The composition of Embodiment 1575, wherein for each plurality independently, a non-random level of all oligonucleotides in the composition that share the same constitution are oligonucleotides of the

plurality.

1578. The composition of any one of Embodiments 1547-1577, wherein for one or two or all pluralities independently, oligonucleotides of the plurality are of the same structure.

1579. The composition of any one of Embodiments 1547-1578, wherein for one or two or all pluralities independently, oligonucleotides of the plurality are each independently a pharmaceutically acceptable salt form.

1580. The composition of any one of Embodiments 1547-1578, wherein for one or two or all pluralities independently, oligonucleotides of the plurality are sodium salts.

1581. The composition of any one of Embodiments 1547-1580, wherein for one or two or all pluralities independently, oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at 10 or more chiral internucleotidic linkages.

1582. The composition of any one of Embodiments 1547-1581, wherein for each plurality independently, oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at 10 or more chiral internucleotidic linkages.

1583. The composition of any one of Embodiments 1547-1582, wherein for one or two or all pluralities independently, oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at each phosphorothioate internucleotidic linkages.

1584. The composition of any one of Embodiments 1547-1583, wherein for each plurality independently, oligonucleotides of the plurality share the same linkage phosphorus stereochemistry at each phosphorothioate internucleotidic linkages.

1585. The composition of any one of Embodiments 1547-1584, wherein for one or two or all pluralities independently, oligonucleotides of the plurality do not share the same linkage phosphorus stereochemistry at one or more or any non-negatively charged internucleotidic linkages.

1586. The composition of any one of Embodiments 1547-1585, wherein for each plurality independently, oligonucleotides of the plurality do not share the same linkage phosphorus stereochemistry at one or more or any non-negatively charged internucleotidic linkages.

1587. A composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are

oligonucleotides of the plurality; and

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of the preceding Embodiments or an acid, base, or salt form thereof.

1588. A composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality; and

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of Embodiments 1637-1662, or an acid, base, or salt form thereof.

1589. A composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality; and

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

1590. The composition of Embodiment 1589, wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid with 0-10 (e.g., 0-1, 0-2, 0-3, 0-4, 0-5, 0-6, 0-7, 0-8, 0-9, 0-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, etc.) mismatches which are not Watson-Crick base pairs.

1591. The composition of Embodiment 1589, wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid with 0-5 mismatches which are not Watson-Crick base pairs.

1592. The composition of Embodiment 1589, wherein the common base sequence is 100% complementary

to a base sequence of a portion of a nucleic acid across the length of the common base sequence except the nucleoside opposite to a target adenosine.

1593. The composition of Embodiment 1589, wherein the common base sequence is 100% complementary to a base sequence of a portion of a nucleic acid across the length of the common base sequence.

1594. The composition of any one of Embodiments 1587-1593, wherein the composition can edit a target A to I when contacted with a nucleic acid in a system expressing ADAR.

1595. The composition of any one of Embodiments 1587-1594, wherein the target adenosine is a G to A mutation associated with a condition, disorder or disease.

1596. The composition of any one of Embodiments 1587-1595, wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type.

1597. A composition comprising a plurality of oligonucleotides, wherein each oligonucleotides of the plurality is independently a particular oligonucleotide or a salt thereof, wherein the particular oligonucleotide is an oligonucleotide of any one of Embodiments 1-1513.

1598. A composition comprising a plurality of oligonucleotides, wherein each oligonucleotides of the plurality is independently a particular oligonucleotide or a salt thereof, wherein the particular oligonucleotide is an oligonucleotide of any one of Embodiments 1-1513, wherein at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition that share the base sequence of a the particular oligonucleotide are oligonucleotide of the plurality.

1599. A composition comprising a plurality of oligonucleotides, wherein each oligonucleotides of the plurality is independently a particular oligonucleotide or a salt thereof, wherein the particular oligonucleotide is an oligonucleotide of any one of Embodiments 1-1513, wherein at least about 5%-100%, 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-100%, 5%-90%, 10%-90%, 20-90%, 30%-90%, 40%-90%, 50%-90%, 5%-85%, 10%-85%, 20-85%, 30%-85%, 40%-85%, 50%-85%, 5%-80%, 10%-80%, 20-80%, 30%-80%, 40%-80%, 50%-80%, 5%-75%, 10%-75%, 20-75%, 30%-75%, 40%-75%, 50%-75%, 5%-70%, 10%-70%, 20-70%, 30%-70%, 40%-70%, 50%-70%, 5%-65%, 10%-65%, 20-65%, 30%-65%, 40%-65%, 50%-65%, 5%-60%, 10%-60%, 20-60%, 30%-60%, 40%-60%, 50%-60%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition that share the constitution of the particular oligonucleotide or a salt thereof are oligonucleotide

of the plurality.

1600. A composition comprising a plurality of oligonucleotides, wherein each oligonucleotides of the plurality is independently a particular oligonucleotide or a salt thereof, wherein the particular oligonucleotide is an oligonucleotide of Table 1.

1601. The composition of any one of Embodiments 1587-1600, wherein a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality.

1602. The composition of any one of Embodiments 1523-1601, wherein the level of oligonucleotides of a plurality in oligonucleotides in the composition that share the common base sequence of the plurality is about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages.

1603. The composition of any one of Embodiments 1523-1601, wherein for each plurality of oligonucleotides, the level of oligonucleotides of the plurality in oligonucleotides in the composition that share the common base sequence of the plurality is independently about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages.

1604. The composition of any one of Embodiments 1523-1601, wherein the level of oligonucleotides of a plurality in oligonucleotides in the composition that share the common constitution of the plurality is about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages.

1605. The composition of any one of Embodiments 1523-1601, wherein for each plurality of oligonucleotides, the level of oligonucleotides of the plurality in oligonucleotides in the composition that share the common constitution of the plurality is independently about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages.

1606. The composition of any one of Embodiments 1523-1605, wherein DS is about 90%-100% (e.g., about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more).

1607. The composition of any one of Embodiments 1602-1606, wherein nc is about 5-40 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40) or more.

1608. The composition of any one of Embodiments 1523-1601, wherein the level is at least about 10%-100%, or at least about 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

1609. The composition of any one of Embodiments 1523-1601, wherein the level is at least about 50%-100%, or at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

1610. A composition comprising a particular oligonucleotide, wherein about 10%-100% (e.g., about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.) of all oligonucleotides in the composition that share the base sequence of the oligonucleotide are independently the particular oligonucleotide or a salt thereof.

1611. A composition comprising a particular oligonucleotide, wherein about 30%-90% of all oligonucleotides in the composition that share the base sequence of the oligonucleotide are independently the particular oligonucleotide or a salt thereof.

1612. A composition comprising a particular oligonucleotide, wherein about 40%-90% of all oligonucleotides in the composition that share the base sequence of the oligonucleotide are independently the particular oligonucleotide or a salt thereof.

1613. The composition of any one of Embodiments 1610-1612, wherein the particular oligonucleotide is an oligonucleotide of any one of Embodiments 1-1521.

1614. The composition of any one of Embodiments 1610-1613, wherein the particular oligonucleotide is an oligonucleotide selected from Table 1.

1615. The composition of any one of Embodiments 1610-1614, wherein the particular oligonucleotide comprises about or at least about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more chiral internucleotidic linkages.

1616. The composition of any one of Embodiments 1610-1615, wherein each salt is independently a pharmaceutically acceptable salt.

1617. The composition of any one of Embodiments 1523-1616, wherein when the composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, the target adenosine residue is modified.

1618. The composition of Embodiment 1617, wherein the modification is or comprises modification performed by ADAR1.

1619. The composition of Embodiment 1617 or 1618, wherein the modification is or comprises modification performed by ADAR2.

1620. The composition of any one of Embodiments 1617-1619, wherein the modification is performed *in vitro*.

1621. The composition of any one of Embodiments 1617-1619, wherein the sample is a cell.

1622. The composition of any one of Embodiments 1617-1621, wherein the target adenosine is converted into inosine.

1623. The composition of any one of Embodiments 1617-1622, wherein the target adenosine is modified to

a greater degree than that is observed with a comparable reference oligonucleotide composition.

1624. The composition of Embodiment 1623, wherein the reference oligonucleotide composition comprises no or a lower level of oligonucleotides of the plurality.

1625. The composition of any one of Embodiments 1623-1624, wherein the reference composition does not contain oligonucleotides that have the same constitution as an oligonucleotide of the plurality.

1626. The composition of any one of Embodiments 1623-1625, wherein the reference composition does not contain oligonucleotides that have the same structure as an oligonucleotide of the plurality.

1627. The composition of Embodiment 1623, wherein the reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of 2'-F modifications compared to oligonucleotides of the plurality.

1628. The composition of any one of Embodiments 1623-1627, wherein the reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of 2'-OMe modifications compared to oligonucleotides of the plurality.

1629. The composition of any one of Embodiments 1623-1628, wherein the reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality have a different sugar modification pattern compared to oligonucleotides of the plurality.

1630. The composition of any one of Embodiments 1623-1629, wherein the reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of modified internucleotidic linkages compared to oligonucleotides of the plurality.

1631. The composition of any one of Embodiments 1623-1630, wherein the reference oligonucleotide composition is a composition whose oligonucleotides having the same base sequence as oligonucleotides of the plurality contain a lower level of phosphorothioate internucleotidic linkages compared to oligonucleotides of the plurality.

1632. The composition of any one of Embodiments 1623-1631, wherein the reference composition is a stereorandom oligonucleotide composition.

1633. The composition of Embodiment 1623, wherein the reference composition is a stereorandom oligonucleotide composition of oligonucleotides of the same constitution as oligonucleotides of the plurality.

1634. The composition of any one of the preceding Embodiments, wherein the composition does not cause significant degradation of the nucleic acid (e.g., no more than about 5%-100% (e.g., no more than about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.)).

1635. The composition of any one of the preceding Embodiments, wherein the composition does not cause

significant exon skipping or altered exon inclusion in the target nucleic acid (e.g., no more than about 5%-100% (e.g., no more than about 10%-100%, 20-100%, 30%-100%, 40%-100%, 50%-80%, 50%-85%, 50%-90%, 50%-95%, 60%-80%, 60%-85%, 60%-90%, 60%-95%, 60%-100%, 65%-80%, 65%-85%, 65%-90%, 65%-95%, 65%-100%, 70%-80%, 70%-85%, 70%-90%, 70%-95%, 70%-100%, 75%-80%, 75%-85%, 75%-90%, 75%-95%, 75%-100%, 80%-85%, 80%-90%, 80%-95%, 80%-100%, 85%-90%, 85%-95%, 85%-100%, 90%-95%, 90%-100%, 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, etc.)).

1636. The composition of any one of Embodiments 1523-1635, wherein the composition is a pharmaceutical composition, and further comprises a pharmaceutically acceptable carrier.

1637. An oligonucleotide, wherein the oligonucleotide is otherwise identical to an oligonucleotide of any one of the preceding Embodiments, except that at a position of a modified internucleotidic linkage is a linkage having the structure of $-O^5-P^L(R^{CA})-O^3-$, wherein:

P^L is P, or P(=W);

W is O, S, or W^N;

R^{CA} is or comprises an optionally substituted or capped chiral auxiliary moiety,

O^5 is an oxygen bonded to a 5'-carbon of a sugar, and

O^3 is an oxygen bonded to a 3'-carbon of a sugar.

1638. The oligonucleotide of Embodiment 1637, wherein the chiral auxiliary is removed the linkage is converted to the modified internucleotidic linkage.

1639. The oligonucleotide of Embodiment 1637, wherein a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

1640. The oligonucleotide of Embodiment 1639, wherein when W is replaced with −SH and R^{CA} is replaced with O, P^L has the same configuration as the linkage phosphorus of the phosphorothioate internucleotidic linkage.

1641. The oligonucleotide of any one of Embodiments 1637-1640, wherein a modified internucleotidic linkage is a neutral internucleotidic linkage.

1642. The oligonucleotide of any one of Embodiments 1637-1640, wherein a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage.

1643. The oligonucleotide of any one of Embodiments 1637-1640, wherein a modified internucleotidic linkage is n004, n008, n025, n026.

1644. The oligonucleotide of any one of Embodiments 1637-1640, wherein a modified internucleotidic linkage is n001.

1645. The oligonucleotide of any one of Embodiments 1637-1644, wherein at each position of a phosphorothioate internucleotidic linkage is independently a linkage having the structure of $-O^5-P^L(W)(R^{CA})-O^3-$.

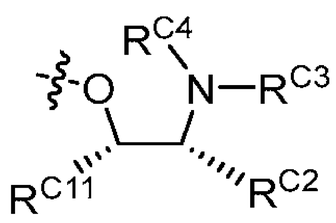
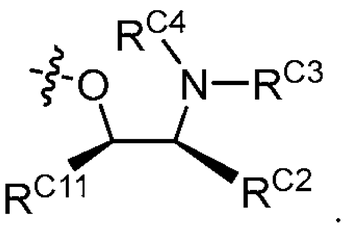
1646. The oligonucleotide of any one of Embodiments 1637-1644, wherein at each position of a modified

internucleotidic linkage is independently a linkage having the structure of $-O^5-P^L(W)(R^{CA})-O^3-$.

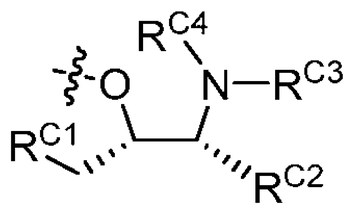
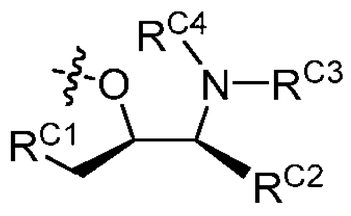
1647. The oligonucleotide of any one of Embodiments 1637-1646, wherein one or each W is S.

1648. The oligonucleotide of any one of Embodiments 1637-1647, wherein one and only one P^L is P.

1649. The oligonucleotide of any one of Embodiments 1637-1648, wherein each R^{CA} is independently


or

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1650. The oligonucleotide of any one of Embodiments 1637-1648, wherein each R^{CA} is independently


or

, wherein R^{C1} is R, $-Si(R)_3$ or $-SO_2R$, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms, R^{C4} is $-H$ or $-C(O)R'$.

1651. The oligonucleotide of Embodiment 1649 or 1650, wherein in a linkage, R^{C4} is $-C(O)R$ and P^L is P.

1652. The oligonucleotide of any one of Embodiments 1650-1651, wherein in a linkage, R^{C4} is $-C(O)R$ and W is S.

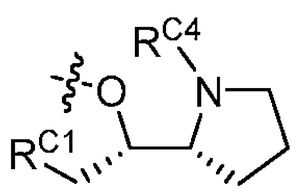
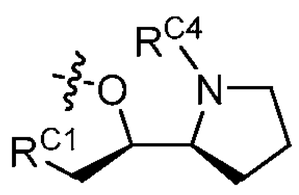
1653. The oligonucleotide of any one of Embodiments 1650-1652, wherein in each linkage wherein W is S, R^{C4} is $-C(O)R'$.

1654. The oligonucleotide of any one of Embodiments 1650-1653, wherein R^{C4} is $-C(O)CH_3$.

1655. The oligonucleotide of Embodiment 1650, wherein in a linkage, R^{C4} is $-H$ and P^L is P.

1656. The oligonucleotide of any one of Embodiments 1650-1655, wherein R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 5-membered ring having no heteroatoms in addition to the nitrogen atom.

1657. The oligonucleotide of any one of Embodiments 1650-1656, wherein each R^{CA} is independently


or

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1658. The oligonucleotide of any one of Embodiments 1650-1657, wherein R^{C1} is $-SiPh_2Me$.

1659. The oligonucleotide of any one of Embodiments 1650-1657, wherein R^{C1} is $-SO_2R$.

1660. The oligonucleotide of any one of Embodiments 1650-1657, wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted C_{1-10} aliphatic.

1661. The oligonucleotide of any one of Embodiments 1650-1657, wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted phenyl.

1662. The oligonucleotide of any one of Embodiments 1650-1657, wherein R^{C1} is $-SO_2R$, wherein R is phenyl.

1663. A phosphoramidite, wherein the nucleobase of the phosphoramidite is a nucleobase of any one of Embodiments 1-1521 or a tautomer thereof, wherein the nucleobase or tautomer thereof is optionally substituted or protected.

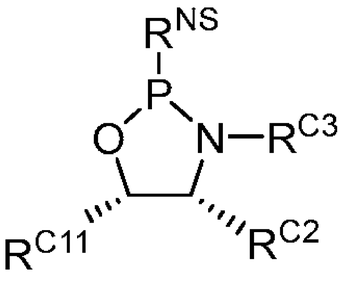
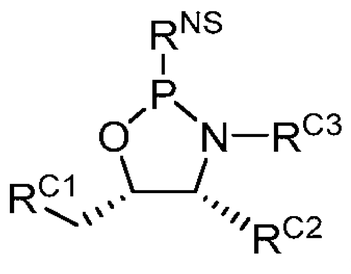
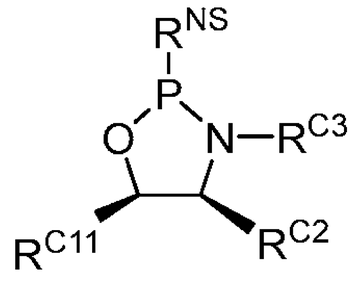
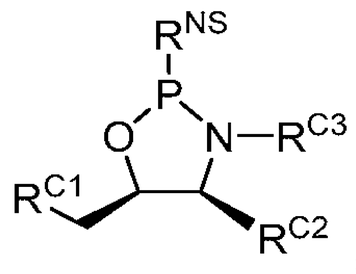
1664. A phosphoramidite, wherein the nucleobase is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

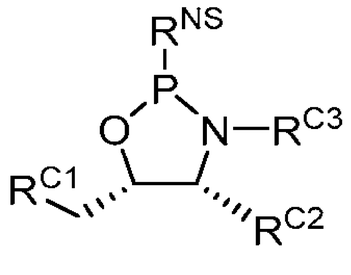
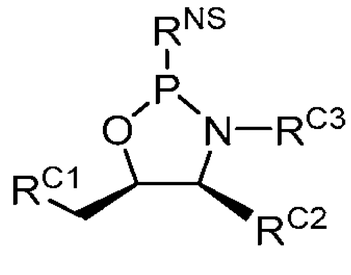
1665. The phosphoramidite of any one of Embodiments 1663-1664, wherein the sugar of the phosphoramidite is a sugar of any one of Embodiments 1-1521, wherein the sugar is optionally protected.

1666. The phosphoramidite of any one of Embodiments 1663-1665, wherein the phosphoramidite has the structure of R^{NS}–P(OR)N$(R)_2$, wherein R^{NS} is a optionally protected nucleoside moiety, and each R is as described herein.

1667. The phosphoramidite of any one of Embodiments 1663-1665, wherein the phosphoramidite has the structure of R^{NS}–P(OCH_2CH_2CN)N(i-Pr)$_2$.

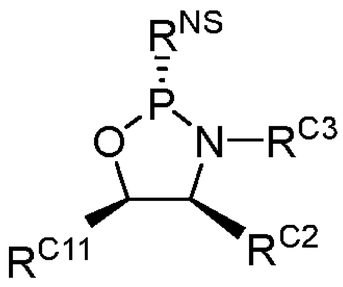
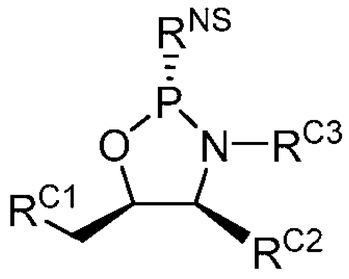
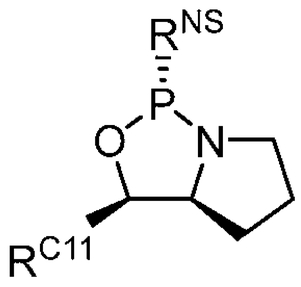
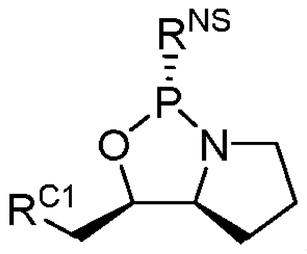
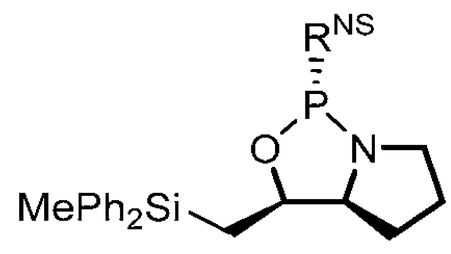
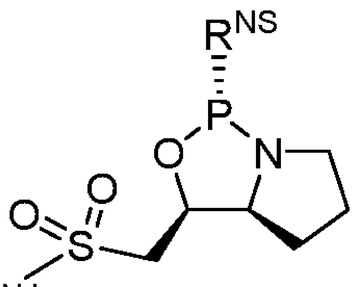
1668. The phosphoramidite of any one of Embodiments 1663-1665, wherein the phosphoramidite comprises a chiral auxiliary moiety, wherein the phosphorus is bonded to an oxygen and a nitrogen atom of the chiral auxiliary moiety.

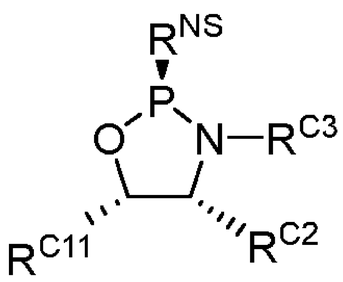
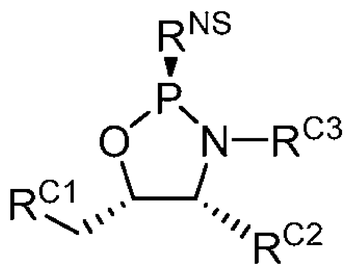
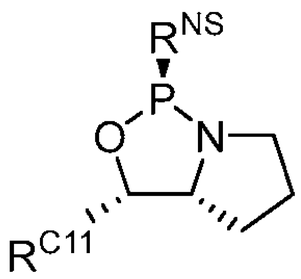
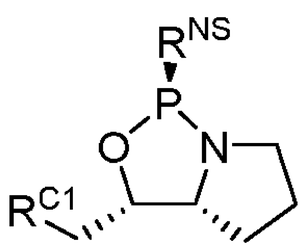
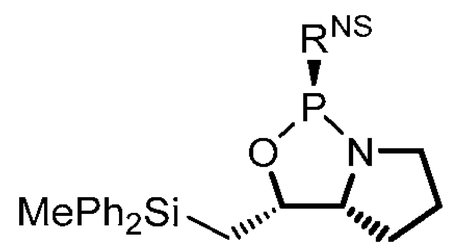
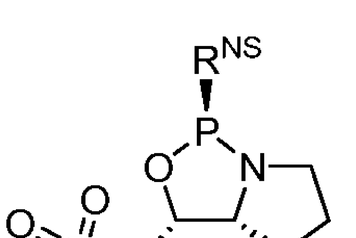
1669. The phosphoramidite of any one of Embodiments 1663-1665 or 1668, wherein the phosphoramidite has the structure of  ,  ,  , or  , or a salt thereof.

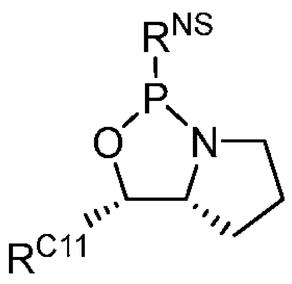
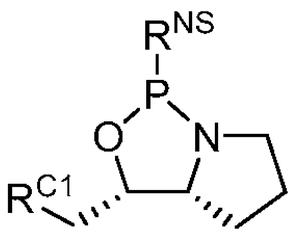
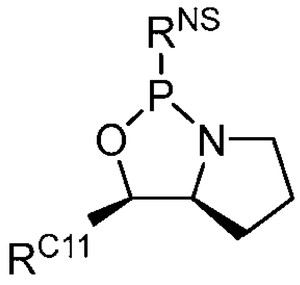
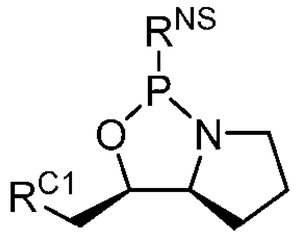
1670. The phosphoramidite of any one of Embodiments 1663-1665 or 1668, wherein the phosphoramidite has the structure of  or  , wherein R^{NS} is a optionally protected nucleoside moiety, R^{C1} is R, –Si$(R)_3$ or –SO_2R, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms.

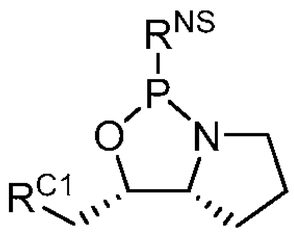
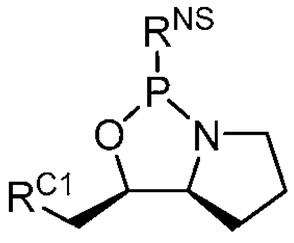
1671. The phosphoramidite of any one of Embodiments 1669-1670, wherein R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 5-membered saturated ring having no heteroatoms in addition to the nitrogen atom.

1672. The phosphoramidite of any one of Embodiments 1669-1671, wherein the phosphoramidite has the

structure of  ,  ,  ,  ,  ,  , or or a salt thereof.

1673. The phosphoramidite of any one of Embodiments 1669-1671, wherein the phosphoramidite has the structure of  ,  ,  ,  ,  ,  , or , or a salt thereof.

1674. The phosphoramidite of any one of Embodiments 1669-1671, wherein the phosphoramidite has the structure of  ,  ,  or  , or a salt thereof.

1675. The phosphoramidite of any one of Embodiments 1669-1671, wherein the phosphoramidite has the structure of  or  .

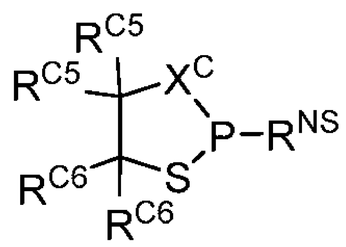
1676. The phosphoramidite of any one of Embodiments 1669-1675, wherein R^{C1} is $-SiPh_2Me$.

1677. The phosphoramidite of any one of Embodiments 1669-1675, wherein R^{C1} is $-SO_2R$.

1678. The phosphoramidite of any one of Embodiments 1669-1675, wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted C_{1-10} aliphatic.

1679. The phosphoramidite of any one of Embodiments 1669-1675, wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted phenyl.

1680. The phosphoramidite of any one of Embodiments 1669-1675, wherein R^{C1} is $-SO_2R$, wherein R is phenyl.

1681. A compound having the structure of  or a salt thereof, wherein R^{NS} is an optionally substituted/protected nucleoside, X^C is O or S, and each of R^{C5} and R^{C6} is independently R.

1682. The compound of Embodiment 1681, wherein X^C is O.

1683. The compound of Embodiment 1681, wherein X^C is S.

1684. The compound of any one of Embodiments 1681-1683, wherein one R^{C5} is not hydrogen.

1685. The compound of any one of Embodiments 1681-1684, wherein one R^{C5} is hydrogen.

1686. The compound of any one of Embodiments 1681-1685, wherein one R^{C6} is not hydrogen.

1687. The compound of any one of Embodiments 1681-1686, wherein one R^{C6} is hydrogen.

1688. The compound of any one of Embodiments 1681-1687, wherein one R^{C5} and one R^{C6} are taken together with their intervening atoms to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 5-10, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) membered monocyclic, bicyclic or polycyclic ring having 0-5 heteroatoms.

1689. The compound of any one of Embodiments 1681-1687, wherein one R^{C5} and one R^{C6} are taken together with their intervening atoms to form an optionally substituted cyclohexyl ring.

1690. The compound of Embodiment 1681, wherein $-X^C-C(R^{C5})_2-C(R^{C6})_2-S-$ is $-OCH(CH_3)CH(CH_3)S-$.

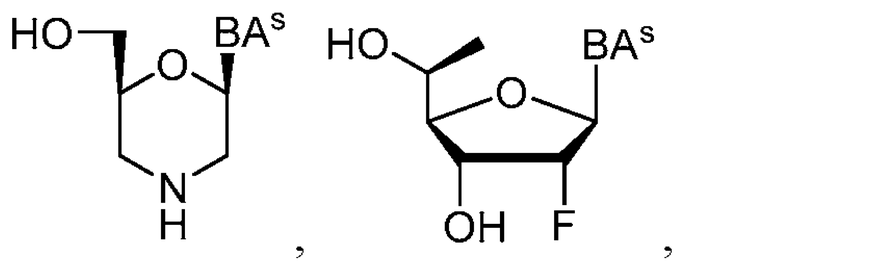
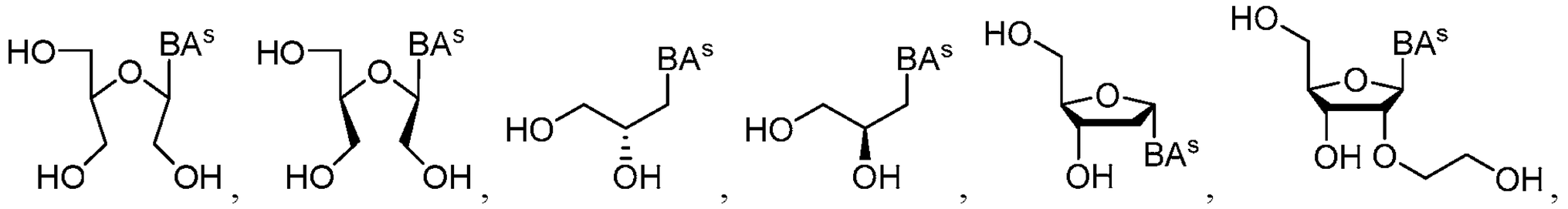
1691. The compound of Embodiment 1681, wherein $-X^C-C(R^{C5})_2-C(R^{C6})_2-S-$ is $-SCH(CH_3)CH(CH_3)S-$.

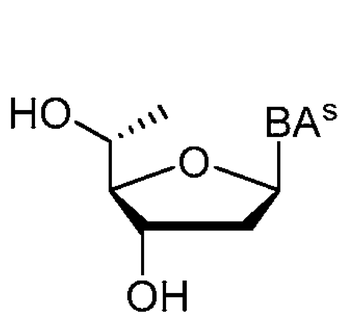
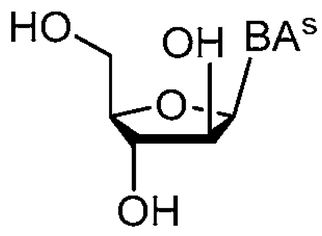
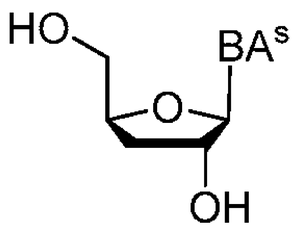
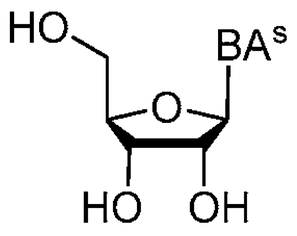
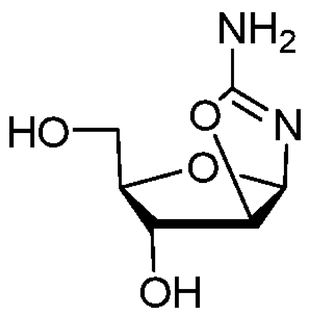
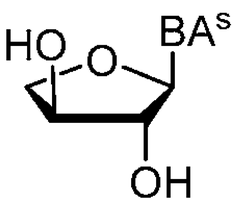
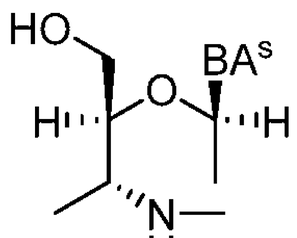
1692. The phosphoramidite or compound of any one of Embodiments 1666-1691, wherein a hydroxyl group of R^{NS} is protected.

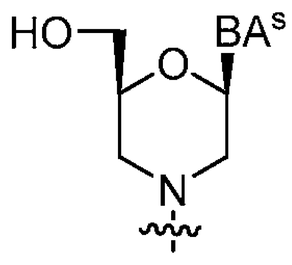
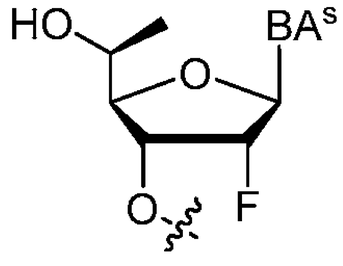
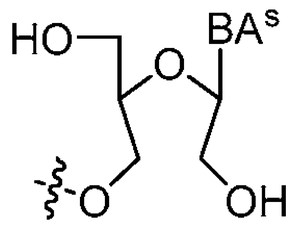
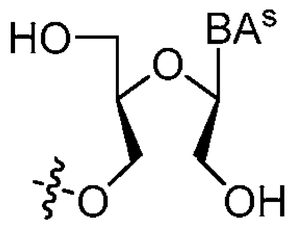
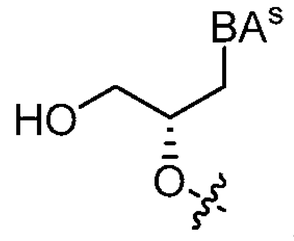
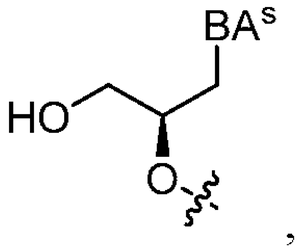
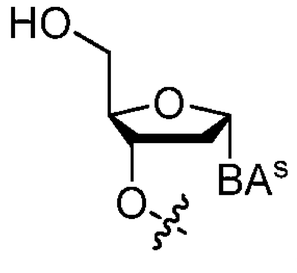
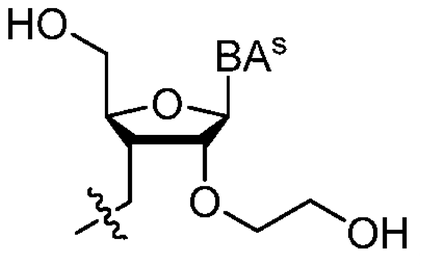
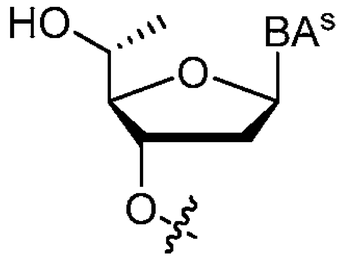
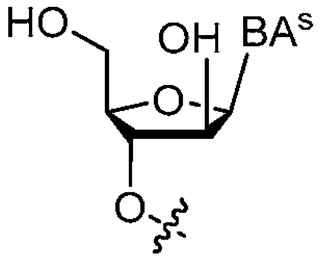
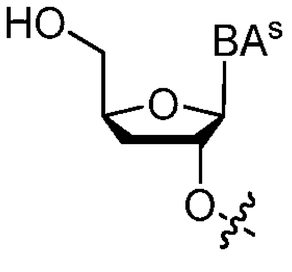
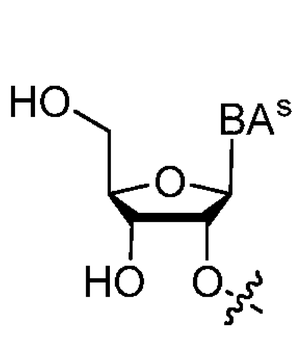
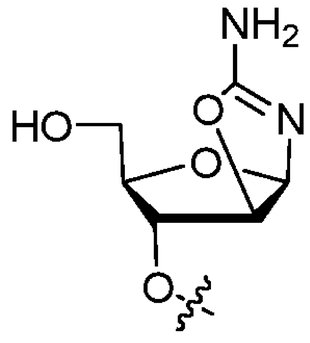
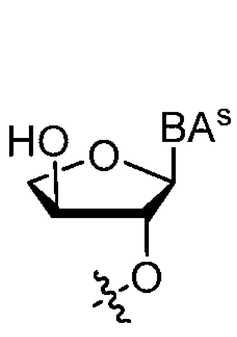
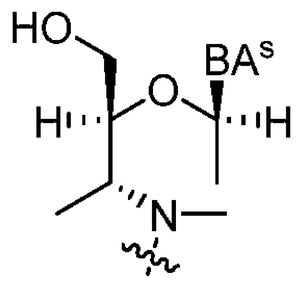
1693. The phosphoramidite or compound of any one of Embodiments 1666-1691, wherein a hydroxyl group of R^{NS} is protected as $-ODMTr$.

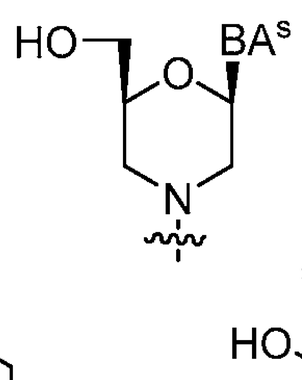
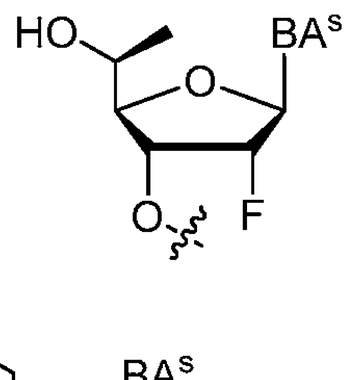
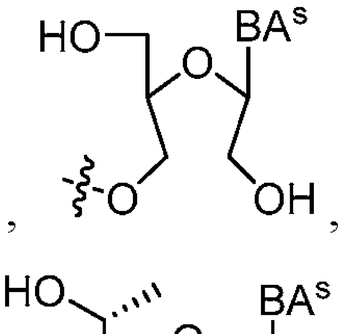
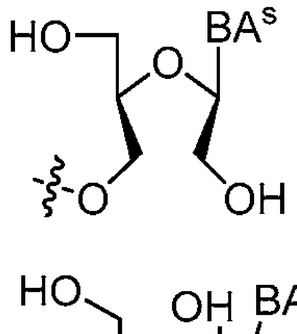
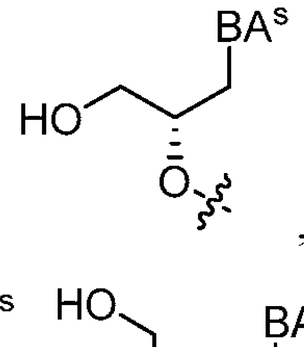
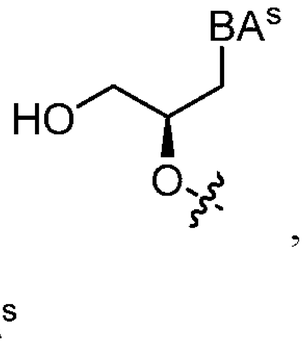
1694. The phosphoramidite or compound of any one of Embodiments 1666-1691, wherein the 5'-OH of R^{NS} is protected.

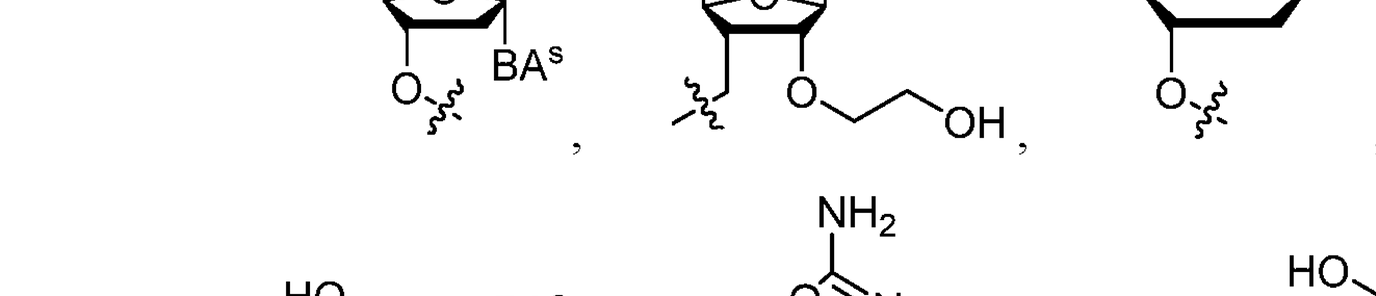
1695. The phosphoramidite or compound of Embodiment 1694, wherein the 5'-OH of R^{NS} is protected as $-ODMTr$.

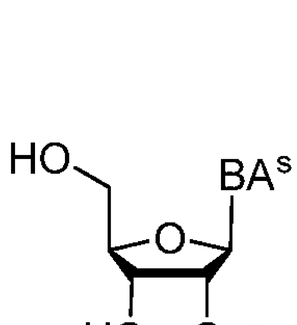
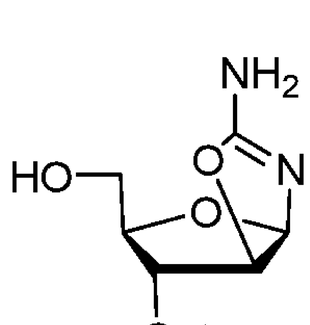
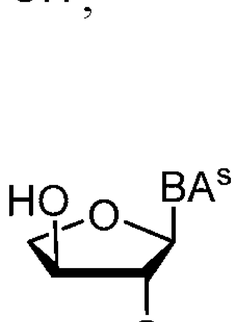
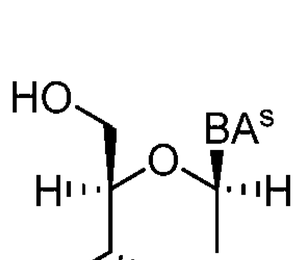
1696. The phosphoramidite or compound of any one of Embodiments 1666-1695, wherein R^{NS} is an optionally substituted or protected nucleoside selected from  , 







, and

, or a salt thereof, wherein BA^s is as described herein.

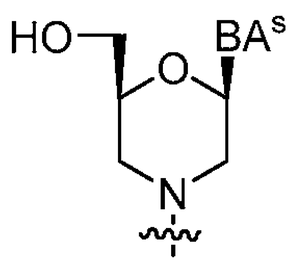
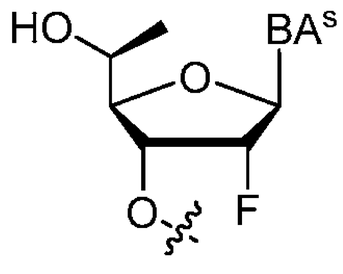
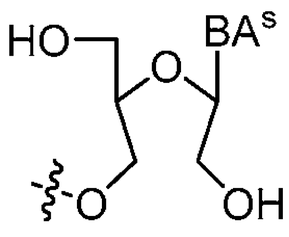
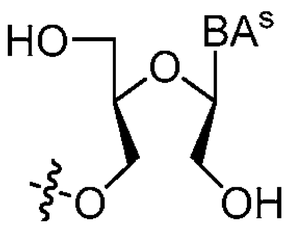
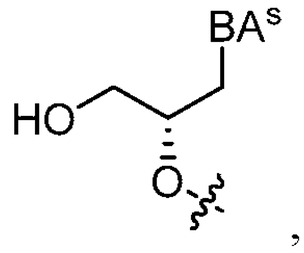
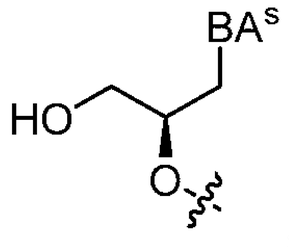
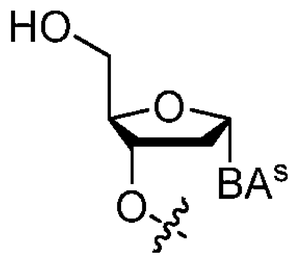
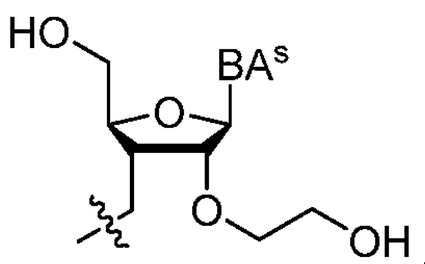
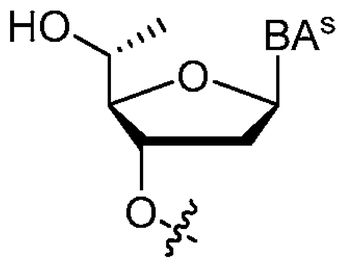
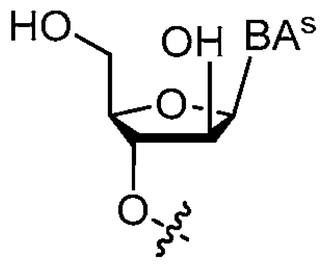
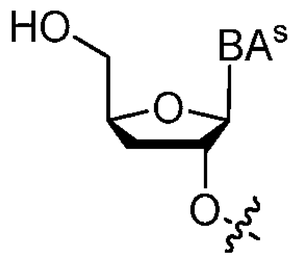
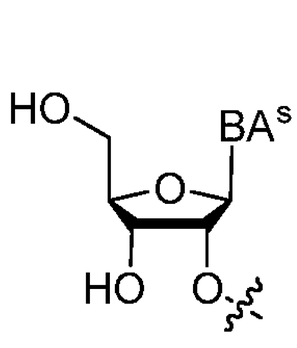
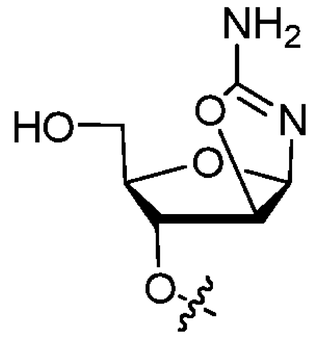
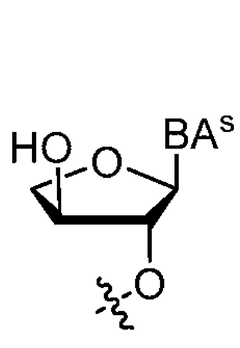
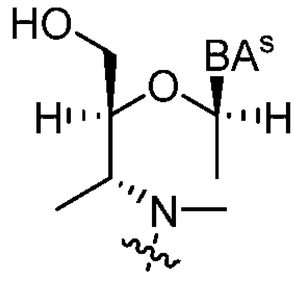
1697. The phosphoramidite or compound of any one of Embodiments 1666-1696, wherein R^{NS} is selected from






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, and

, or a salt thereof, wherein BA^s is as described herein.

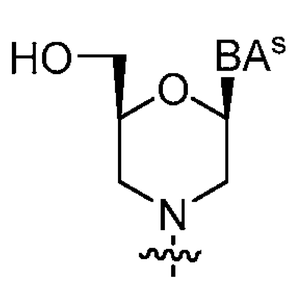
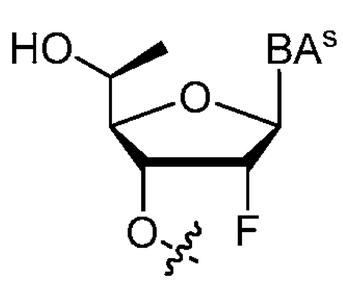
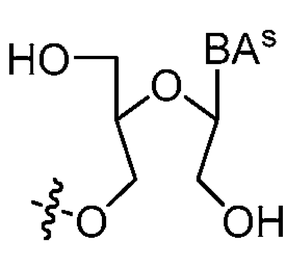
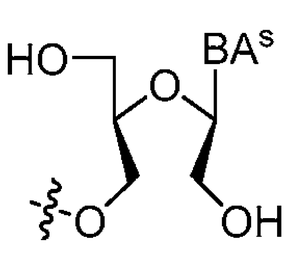
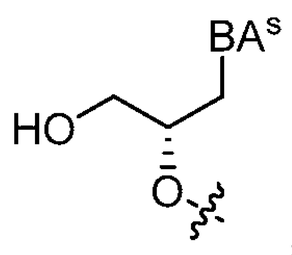
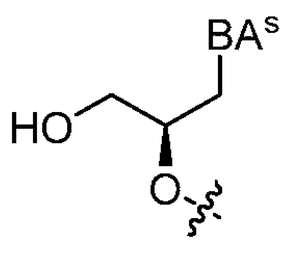
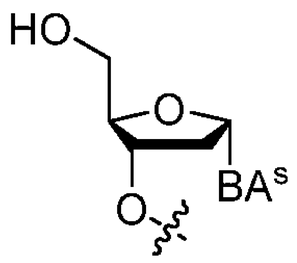
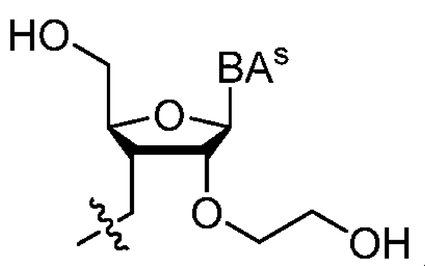
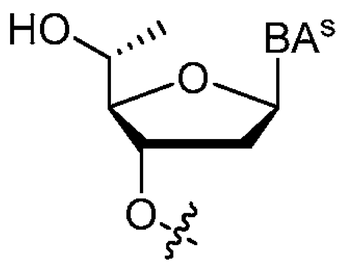
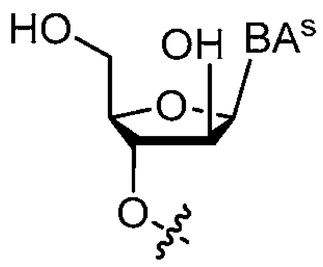
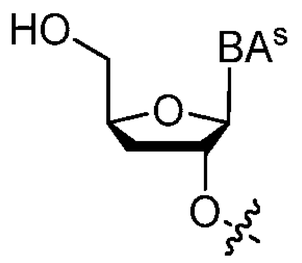
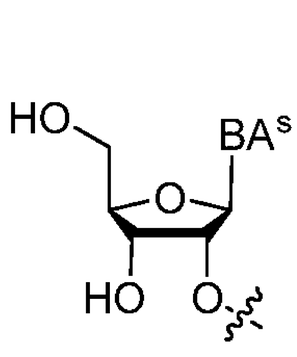
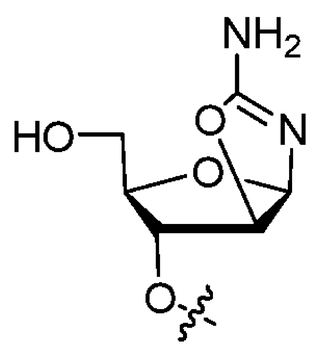
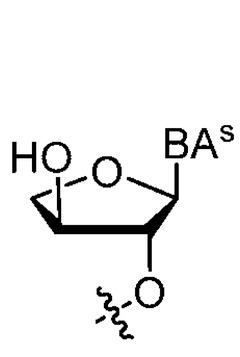
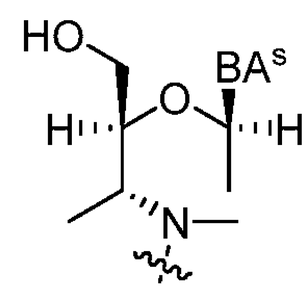
1698. The phosphoramidite or compound of any one of Embodiments 1666-1697, wherein R^{NS} is selected from






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, and

, or a salt thereof, wherein BA^s is

optionally substituted or protected nucleobase, and each −OH is optionally and independently substituted or protected.

1699. The phosphoramidite or compound of any one of Embodiments 1666-1698, wherein R^{NS} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , or a salt thereof, wherein BA^s is optionally substituted or protected nucleobase, and each −OH of the nucleoside is independently protected, wherein at least one −OH is protected as DMTrO−.

1700. The phosphoramidite or compound of any one of Embodiments 1666-1699, wherein R^{NS} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , or a salt thereof, wherein BA^s is an optionally protected nucleobase selected from A, T, C, G, U, and tautomers thereof, and each −OH of the nucleoside is independently protected, wherein at least one −OH is protected as DMTrO−.

1701. The phosphoramidite or compound of any one of Embodiments 1666-1700, wherein the phosphoramidite or compound comprises a nucleobase of any one of Embodiments 1-1521 or a tautomer thereof, wherein the nucleobase or tautomer thereof is optionally substituted or protected.

1702. The phosphoramidite or compound of any one of Embodiments 1666-1701, wherein the phosphoramidite or compound comprises a nucleobase, wherein the nucleobase is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

1703. The phosphoramidite or compound of any one of Embodiments 1666-1702, wherein the phosphoramidite or compound comprises a nucleobase, wherein the nucleobase is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

1704. The phosphoramidite or compound of any one of Embodiments 1666-1703, wherein BA^s has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

1705. The phosphoramidite or compound of any one of Embodiments 1666-1701, wherein the phosphoramidite or compound comprises hypoxanthine.

1706. The phosphoramidite or compound of any one of Embodiments 1666-1701, wherein the phosphoramidite or compound comprises O^6-protected hypoxanthine.

1707. The phosphoramidite or compound of any one of Embodiments 1666-1701, wherein the phosphoramidite or compound comprises O^6-protected hypoxanthine, wherein the O^6 protection group is $-CH_2CH_2Si(R)_3$, wherein the $-CH_2CH_2-$ is optionally substituted and each R is not –H.

1708. The phosphoramidite or compound of any one of Embodiments 1666-1701, wherein the phosphoramidite or compound comprises O^6-protected hypoxanthine, wherein the O^6 protection group is $-CH_2CH_2Si(Me)_3$.

1709. The phosphoramidite or compound of any one of Embodiments 1666-1708, wherein the phosphoramidite or compound comprises a sugar which is a sugar of any one of Embodiments 1-1521.

1710. The phosphoramidite or compound of any one of Embodiments 1666-1695, wherein R^{NS} is an optionally substituted or protected nucleoside selected from A, T, C, G and U.

1711. The phosphoramidite or compound of any one of Embodiments 1666-1695, wherein R^{NS} is an optionally substituted or protected nucleoside selected from b001U, b002U, b003U, b004U, b005U, b006U, b008U, b002A, b001G, b004C, b007U, b001A, b001C, b002C, b003C, b002I, b003I, b009U, b003A, b007C, Asm01, Gsm01, 5MSfC, Usm04, 5MRdT, Csm15, Csm16, rCsm14, Csm17 and Tsm18.

1712. The phosphoramidite or compound of any one of Embodiments 1666-1711, wherein R^{NS} is bonded to phosphorus through its 3’-O-.

1713. The phosphoramidite or compound of any one of Embodiments 1669-1712, wherein the purity of the phosphoramidite is at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

1714. A method for preparing an oligonucleotide or composition, comprising coupling a −OH group of an oligonucleotide or a nucleoside with a phosphoramidite or compound of any one of Embodiments 1663-1713.

1715. A method for preparing an oligonucleotide or composition, comprising coupling a 5'-OH of an oligonucleotide or a nucleoside with a phosphoramidite or compound of any one of Embodiments 1663-1713.

1716. A method for preparing an oligonucleotide or composition, comprising removing a chiral auxiliary moiety from an oligonucleotide of any one of Embodiments 1523-1662.

1717. The method of any one of Embodiments 1714-1716, wherein the oligonucleotide, or an oligonucleotide in the composition, comprises a sugar comprising 2'-OH.

1718. The method of any one of Embodiments 1714-1717, wherein the oligonucleotide, or an oligonucleotide in the composition, comprises a sugar comprising 2'-OH, wherein the sugar is bonded to a chirally controlled internucleotidic linkage.

1719. The oligonucleotide, composition or method of any one of the preceding Embodiments, wherein each heteroatom is independently selected from nitrogen, oxygen, silicon, phosphorus and sulfur.

1720. The oligonucleotide, composition or method of any one of the preceding Embodiments, wherein each nucleobase independently comprises an optionally substituted ring having at least one nitrogen.

1721. A method, comprising:

assessing an agent or a composition thereof in a cell, tissue or animal, wherein the cell, tissue or animal is or comprises a cell, tissue or organ associated or of a condition, disorder or disease, and/or comprises a nucleotide sequence associated with a condition, disorder or disease; and

administering to a subject susceptible to or suffering from a condition, disorder or disease an effective amount of an agent or a composition for preventing or treating the condition, disorder or disease.

1722. A method, comprising:

administering to a subject susceptible to or suffering from a condition, disorder or disease an effective amount of an agent or a composition for preventing or treating the condition, disorder or disease, wherein the agent or composition is assessed in a cell, tissue or animal, wherein the cell, tissue or animal is or comprises a cell, tissue or organ associated or of a condition, disorder or disease, and/or comprises a nucleotide sequence associated with a condition, disorder or disease.

1723. The method of Embodiment 1721-1722, wherein the subject is a human.

1724. The method of any one of Embodiments 1721-1723, wherein a condition, disorder or disease is associated with a G to A mutation.

1725. The method of any one of Embodiments 1721-1724, wherein a condition, disorder or disease is associated with 1024 G>A (E342K) mutation in human SERPINA1 gene.

1726. The method of any one of Embodiments 1721-1725, wherein a condition, disorder or disease is alpha-1 antitrypsin deficiency.

1727. The method of any one of Embodiments 1721-1723, wherein a condition, disorder or disease is cancer.

1728. A method for characterizing an oligonucleotide or a composition, comprising:

administering the oligonucleotide or composition to a cell or a population thereof comprising or expressing an ADAR1 polypeptide or a characteristic portion thereof, or a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

1729. The method of any one of Embodiments 1721-1728, wherein a cell is a rodent cell.

1730. The method of any one of Embodiments 1721-1728, wherein a cell is a rat cell.

1731. The method of any one of Embodiments 1721-1728, wherein a cell is a mouse cell.

1732. The method of any one of Embodiments 1721-1731, wherein the genome of the cell comprises a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

1733. A method for characterizing an oligonucleotide or a composition, comprising:

administering the oligonucleotide or composition to a non-human animal or a population thereof comprising or expressing an ADAR1 polypeptide or a characteristic portion thereof, or a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

1734. The method of Embodiment 1733, wherein the animal is a mouse.

1735. The method of any one of Embodiments 1733-1734, wherein the genome of the animal comprises a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

1736. The method of any one of Embodiments 1733-1734, wherein the germline genome of the animal comprises a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

1737. The method of any one of Embodiments 1721-1736, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises one or both of human ADAR1 Z-DNA binding domains.

1738. The method of any one of Embodiments 1721-1737, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises one or more or all of human ADAR1 dsRNA binding domains.

1739. The method of any one of Embodiments 1721-1738, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises human deaminase domain.

1740. The method of any one of Embodiments 1721-1739, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1.

1741. The method of any one of Embodiments 1721-1740, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1 p110.

1742. The method of any one of Embodiments 1721-1740, wherein an ADAR1 polypeptide or a characteristic portion thereof is or comprises human ADAR1 p150.

1743. The method of any one of Embodiments 1721-1742, wherein activity levels of an oligonucleotide or composition observed from a cell or a cell from an animal, or a population thereof, is more similar to those observed in a comparable human cell or a population thereof compared to those observed in a cell prior to engineering or a cell from an animal prior to engineering, or a population thereof.

1744. The method of Embodiment 1743, wherein a comparable human cell is of the same type as a cell or a cell from an animal.

1745. The method of any one of Embodiments 1721-1744, wherein the cell, tissue or animal is or comprises a cell, tissue or organ associated with or of a condition, disorder or disease.

1746. The method Embodiment 1745, wherein a cell, tissue or organ associated with or of a condition, disorder or disease is or comprises a tumor.

1747. The method of any one of Embodiments 1721-1746, wherein the cell, tissue or animal comprises a nucleotide sequence associated with a condition, disorder or disease.

1748. The method of Embodiment 1747, wherein a nucleotide sequence associated with a condition, disorder or disease is homozygous.

1749. The method of Embodiment 1747, wherein a nucleotide sequence associated with a condition, disorder or disease is heterozygous.

1750. The method of Embodiment 1747, wherein a nucleotide sequence associated with a condition, disorder or disease is hemizygous.

1751. The method of any one of Embodiments 1747-1750, wherein a nucleotide sequence associated with a condition, disorder or disease is in a genome.

1752. The method of any one of Embodiments 1747-1751, wherein a nucleotide sequence associated with a condition, disorder or disease is in a genome of some but not all cells.

1753. The method of any one of Embodiments 1747-1752, wherein a nucleotide sequence associated with a condition, disorder or disease is in a germline genome.

1754. The method of any one of Embodiments 1747-1753, wherein a nucleotide sequence associated with a condition, disorder or disease is a mutation.

1755. The method of any one of Embodiments 1747-1754, wherein a nucleotide sequence associated with a condition, disorder or disease is a G to A mutation.

1756. The method of any one of Embodiments 1747-1755, wherein a nucleotide sequence associated with a condition, disorder or disease is a G to A mutation in SERPINA1.

1757. The method of any one of Embodiments 1747-1756, wherein a nucleotide sequence associated with a condition, disorder or disease is a 1024 G>A (E342K) mutation in human SERPINA1.

1758. The method of any one of Embodiments 1721-1756, wherein the cell, tissue or animal comprises a 1024 G>A (E342K) mutation in human SERPINA1 gene.

1759. The method of Embodiment 1758, wherein the cell, tissue or animal comprises NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ.

1760. The method of any one of Embodiments 1721-1759, wherein the subject comprises 1024 G>A (E342K) mutation in human SERPINA1.

1761. The method of Embodiment 1760, wherein the subject is homozygous with respect to 1024 G>A (E342K) mutation in human SERPINA1.

1762. The method of Embodiment 1760, wherein the subject is heterozygous with respect to 1024 G>A (E342K) mutation in human SERPINA1.

1763. The method of Embodiment 1760, wherein the subject is heterozygous with respect to 1024 G>A (E342K) mutation in SERPINA1, and one allele is wild type.

1764. A method for modifying a target adenosine in a target nucleic acid, comprising contacting the target nucleic acid with an oligonucleotide or composition of any one of the preceding Embodiments.

1765. A method for deaminating a target adenosine in a target nucleic acid, comprising contacting the target nucleic acid with an oligonucleotide or composition of any one of the preceding Embodiments.

1766. A method for producing, or restoring or increasing level of a product of a particular nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition of any one of the preceding Embodiments, wherein the target nucleic acid comprises a target adenosine, and the particular nucleic acid differs from the target nucleic acid in that the particular nucleic acid has an I or G instead of the target adenosine.

1767. A method for reducing level of a product of a target nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition of any one of the preceding Embodiments, wherein the target nucleic acid comprises a target adenosine.

1768. The method of Embodiment 1766 or 1767, wherein the product is a protein.

1769. The method of Embodiment 1766 or 1767, wherein the product is a mRNA.

1770. The method of any one of Embodiments 1764-1769, wherein the base sequence the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of the target nucleic acid.

1771. The method of any one of Embodiments 1764-1770, wherein the target nucleic acid is in a sample.

1772. A method, comprising:

contacting an oligonucleotide or composition of any one of the preceding Embodiments with a sample comprising a target nucleic acid and an adenosine deaminase, wherein:

the base sequence of the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of the target nucleic acid; and

the target nucleic acid comprises a target adenosine;

wherein the target adenosine is modified.

1773. A method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which

level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

1774. A method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality.

1775. A method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially

complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

1776. A method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality.

1777. A method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic

linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition); and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition.

1778. A method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition).

1779. The method of any one of Embodiments 1773-1778, wherein a first oligonucleotide composition is an oligonucleotide composition of any one of the preceding Embodiments.

1780. The method of any one of Embodiments 1773-1779, wherein the reference oligonucleotide composition is a reference oligonucleotide composition of any one of Embodiments 1624-1633.

1781. The method of any one of Embodiments 1764-1780, wherein the deaminase is an ADAR enzyme.

1782. The method of any one of Embodiments 1764-1780, wherein the deaminase is ADAR1.

1783. The method of any one of Embodiments 1764-1780, wherein the deaminase is ADAR2.

1784. The method of any one of Embodiments 1764-1783, wherein the target nucleic acid is or comprise RNA.

1785. The method of any one of Embodiments 1764-1784, wherein a sample is a cell.

1786. The method of any one of Embodiments 1764-1785, wherein the target nucleic acid is more associated with a condition, disorder or disease, or decrease of a desired property or function, or increase of an undesired property or function, compared to a nucleic acid which differs from the target nucleic acid in that it has an I or G at the position of the target adenosine instead of the target adenosine.

1787. The method of any one of Embodiments 1764-1785, wherein the target adenosine is a G to A mutation.

1788. A method for preventing or treating a condition, disorder or disease, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1789. A method for preventing or treating a condition, disorder or disease amenable to a G to A mutation, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1790. A method for preventing or treating a condition, disorder or disease amenable to a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1791. A method for increasing levels and/or activities of an alpha-1 antitrypsin (A1AT) polypeptide in the serum or blood of a subject, comprising administering to the subject an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1792. The method of Embodiment 1791, wherein the A1AT polypeptide provides one or more higher activities compared to a reference A1AT polypeptide.

1793. The method of Embodiment 1791 or 1792, wherein the A1AT polypeptide is a wild-type A1AT polypeptide.

1794. The method of any one of Embodiments 1791-1793, wherein the method increase the amount of the A1AT polypeptide in serum.

1795. The method of any one of Embodiments 1791-1793, wherein the method decrease the amount of a reference A1AT polypeptide in serum.

1796. The method of any one of Embodiments 1791-1795, wherein the method increase the ratio of the A1AT polypeptide over a reference A1AT polypeptide in serum or blood.

1797. The method of any one of Embodiments 1791-1796, wherein the reference A1AT polypeptide is mutated.

1798. The method of any one of Embodiments 1791-1797, wherein the reference A1AT polypeptide is an E342K A1AT polypeptide.

1799. A method for decreasing levels and/or activities of a mutant alpha-1 antitrypsin (A1AT) polypeptide in the serum or blood of a subject, comprising administering to the subject an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1800. The method of Embodiment 1799, wherein the mutant A1AT polypeptide is an E342K A1AT polypeptide.

1801. The method of any one of Embodiments 1791-1800, wherein the subject is susceptible to or suffering from a condition, disorder or disease.

1802. A method for preventing or treating a condition, disorder or disease associated with a G to A

mutation, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1803. A method for preventing or treating a condition, disorder or disease associated with a G to A mutation, comprising administering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1804. The method of any one of Embodiments 1788-1803, wherein the base sequence of the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of the target nucleic acid comprising a target adenosine that is the mutation.

1805. The method of any one of Embodiments 1803-1804, wherein the condition, disorder or disease is amenable to an A to G or A to I modification.

1806. The method of any one of Embodiments 1788-1805, wherein cells associated with the condition, disorder or disease comprise or express an ADAR protein.

1807. The method of any one of Embodiments 1788-1805, wherein cells associated with the condition, disorder or disease comprise or express ADAR1.

1808. The method of any one of Embodiments 1788-1805, wherein cells associated with the condition, disorder or disease comprise or express ADAR2.

1809. The method of any one of Embodiments 1788-1808, wherein the subject is a human subject.

1810. The method of any one of Embodiments 1788-1809, wherein the condition, disorder or disease is or is associated with alpha-1 antitrypsin deficiency.

1811. The method of any one of Embodiments 1764-1810, comprising converting a target adenosine to I.

1812. The method of any one of Embodiments 1764-1811, wherein two or more different adenosine are targeted and edited.

1813. The method of any one of Embodiments 1764-1811, wherein two or more different transcripts are targeted and edited.

1814. The method of any one of Embodiments 1764-1811, wherein transcripts from two or more different polynucleotides are targeted and edited.

1815. The method of any one of Embodiments 1764-1811, wherein transcripts from two or more genes are targeted and edited.

1816. The method of any one of Embodiments 1812-1815, comprising administering two or more oligonucleotides, each of which independently targets a different target, and each of which is independently an oligonucleotide of any one of Embodiments 1-1521 or a salt thereof.

1817. The method of any one of Embodiments 1812-1815, comprising administering two or more oligonucleotide compositions, each of which independently targets at least one different target, and each of which is independently a composition of any one of Embodiments 1522-1636.

1818. The method of any one of Embodiments 1812-1817, comprising administering a composition of any one of Embodiments 1547-1636.

1819. The method of any one of Embodiments 1812-1818, wherein two or more oligonucleotides or compositions are administered concurrently.

1820. The method of any one of Embodiments 1812-1819, wherein two or more oligonucleotides or compositions are administered concurrently in a single composition.

1821. The method of any one of Embodiments 1812-1819, wherein two or more oligonucleotides or compositions are administered as separated compositions.

1822. The method of any one of Embodiments 1812-1818, wherein one or more oligonucleotides or compositions are administered prior or subsequently to one or more other oligonucleotides or compositions.

1823. The method of any one of Embodiments 1788-1822, wherein the subject comprises 1024 G>A (E342K) mutation in human SERPINA1.

1824. The method of Embodiment 1823, wherein the subject is homozygous with respect to 1024 G>A (E342K) mutation in human SERPINA1.

1825. The method of Embodiment 1823, wherein the subject is heterozygous with respect to 1024 G>A (E342K) mutation in human SERPINA1.

1826. The method of Embodiment 1823, wherein the subject is heterozygous with respect to 1024 G>A (E342K) mutation in human SERPINA1, and one allele is wild type.

1827. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is associated with a G to A mutation in SERPINA1.

1828. The method of any one of Embodiments 1788-1827, wherein the condition, disorder or disease is associated with 1024 G>A (E342K) mutation in human SERPINA1.

1829. The method of any one of Embodiments 1788-1828, wherein the condition, disorder or disease is alpha-1 antitrypsin deficiency.

1830. The method of any one of Embodiments 1788-1829, wherein the subject has a heterozygous ZZ genotype.

1831. The method of any one of Embodiments 1788-1829, wherein the subject has a homozygous ZZ genotype.

1832. The method of any one of Embodiments 1788-1831, wherein the method increase or restores level or activity of wild-type at liver.

1833. The method of any one of Embodiments 1788-1832, wherein the method reduces Z-AAT aggregation.

1834. The method of any one of Embodiments 1788-1833, wherein the method reduces or prevents liver damage.

1835. The method of any one of Embodiments 1788-1834, wherein the method reduces or prevents cirrhosis.

1836. The method of any one of Embodiments 1788-1835, wherein the method increase level of wild-type AAT in blood.

1837. The method of any one of Embodiments 1788-1836, wherein the method increase level of circulating, lung-bound wild-type AAT in blood.

1838. The method of any one of Embodiments 1788-1837, wherein the method reduces or prevents lung damage.

1839. The method of any one of Embodiments 1788-1838, wherein the method reduces or prevents lung damage from protease.

1840. The method of any one of Embodiments 1788-1839, wherein the method reduces or prevents lung inflammation.

1841. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a recessive or dominant genetically defined condition, disorder or disease.

1842. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a liver condition, disorder or disease.

1843. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a metabolic liver condition, disorder or disease.

1844. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a neuronal condition, disorder or disease.

1845. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a neurodevelopmental condition, disorder or disease.

1846. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a condition, disorder or disease associated with ion channel permeability.

1847. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is familial epilepsies.

1848. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is neuropathic pain.

1849. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a haploinsufficient condition, disorder or disease.

1850. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is a neuromuscular condition, disorder or disease.

1851. The method of any one of Embodiments 1788-1826, wherein the condition, disorder or disease is dementias.

1852. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject comprise targeting moieties.

1853. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject comprise targeting moieties that target liver.

1854. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject comprise one or more ligands targeting one or more receptors expressed in liver.

1855. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject comprise one or more ligands targeting an asialoglycoprotein receptor.

1856. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject are GalNAc-conjugated oligonucleotides.

1857. The method of any one of Embodiments 1788-1851, wherein oligonucleotides administered to the subject comprise one or more ligands targeting one or more receptors expressed in liver.

1858. Use of an oligonucleotide or composition of any one of the preceding Embodiments for alter mRNA splicing, wherein a target adenosine of an mRNA is edited.

1859. The use of Embodiment 1860, wherein an exon is skipped, or an exon is included, or frame is restored.

1860. Use of an oligonucleotide or composition of any one of the preceding Embodiments for alter mRNA splicing, wherein a target adenosine of an mRNA is edited.

1861. The use of Embodiment 1860, wherein levels of a RNA and/or a polypeptide encoded thereby is reduced.

1862. Use of an oligonucleotide or composition of any one of the preceding Embodiments for silencing protein expression, wherein a target adenosine of an mRNA encoding the protein is edited.

1863. The use of Embodiment 1862, wherein expression, level and/or activity of a protein is increased or restored.

1864. Use of an oligonucleotide or composition of any one of the preceding Embodiments for fixing nonsense mutation, wherein a target adenosine of an RNA is edited so that the nonsense mutation is fixed.

1865. The use of Embodiment 1864, wherein expression, level and/or activity of a protein is increased or restored.

1866. Use of an oligonucleotide or composition of any one of the preceding Embodiments for fixing missense mutation, wherein a target adenosine of an RNA is edited so that the missense mutation is fixed.

1867. The use of Embodiment 1866, wherein expression, level and/or activity of a protein is increased or restored.

1868. Use of an oligonucleotide or composition of any one of the preceding Embodiments for editing a target adenosine in a codon.

1869. The use of Embodiment 1868, wherein sequence, expression, level and/or activity of a protein is altered.

1870. Use of an oligonucleotide or composition of any one of the preceding Embodiments for editing a target adenosine in an upstream ORF.

1871. The use of Embodiment 1870, wherein expression, level and/or activity of a protein is increased.

1872. A method for modulating protein-protein interaction in a system wherein a protein is translated from its encoding RNA, comprising contacting the encoding RNA with an oligonucleotide or composition of any one of the preceding Embodiments, wherein an adenosine in the encoding RNA is edited, wherein a protein

is translated from the encoded mRNA ("the edited protein"), wherein the edited protein differs from the unedited protein at an amino acid residue involving in the protein-protein interaction.

1873. A method for modulating an interaction between a protein and its partner protein in a system, comprising administering to the system of any one of the preceding Embodiments, wherein the oligonucleotide or composition is capable of editing an adenosine in a nucleic acid encoding the protein or its partner protein, and an edited nucleic acid encodes a protein that is different from the protein encoded by the unedited nucleic acid at at least one amino acid residue involved in the interaction between the protein and its partner protein.

1874. The method of any one of Embodiments 1872-1873, wherein the edited adenosine is in a codon encoding an amino acid residue involved in the interaction between the protein and its partner protein.

1875. The method of any one of Embodiment 1874, wherein the edited adenosine is in a codon encoding an amino acid residue involved in the interaction between the protein and its partner, and the editing changed the amino acid to a different amino acid.

1876. The method of any one of Embodiments 1872-1875, wherein the protein-protein interaction is reduced or disrupted.

1877. The method of any one of Embodiments 1872-1876, wherein the protein is a transcription factor.

1878. The method of any one of Embodiments 1872-1877, wherein level of the protein is increased.

1879. The method of any one of Embodiments 1872-1878, wherein expression of one or more nucleic acids regulated by the protein is modulated.

1880. The method of any one of Embodiments 1872-1879, wherein expression of one or more nucleic acids regulated by the protein is increased.

1881. The method of any one of Embodiments 1872-1880, wherein the protein is NRF2.

1882. The method of any one of Embodiments 1872-1881, wherein editing of NRF2 is or comprises editing a codon encoding Glu82 (e.g., to Gly), Glu79 (e.g., to Gly), Glu78 (e.g., to Gly), Asp76 (e.g., to Gly), Ile28 (to Val), Asp27 (e.g., to Gly), or Gln26 (e.g., to Arg).

1883. The method of any one of Embodiments 1872-1882, wherein the partner protein is Keap1.

1884. The method of any one of Embodiments 1872-1883, wherein editing of Keap1 is or comprises editing a codon encoding Ser603 (e.g., to Gly), Tyr572 (e.g., to Cys), Tyr525 (e.g., to Cys), Ser508 (e.g., to Gly), His436 (e.g., to Arg), Asn382 (e.g., to Asp), Arg380 (e.g., to Gly), or Tyr334.

1885. The method of any one of Embodiments 1872-1883, wherein the system is or comprises a cell.

1886. The method of any one of Embodiments 1872-1883, wherein the system is or comprises a tissue.

1887. The method of any one of Embodiments 1872-1883, wherein the system is or comprises an organ.

1888. The method of any one of Embodiments 1872-1883, wherein the system is or comprises an organism.

1889. A method for editing a transcript in an immune cell, comprising administering to an immune cell an effective amount of an oligonucleotide or composition of any one of the preceding Embodiments.

1890. The method of Embodiment 1889, wherein an immune cell is a PBMC.

1891. The method of Embodiment 1889, wherein an immune cell is a CD4+ cell.

1892. The method of Embodiment 1889, wherein an immune cell is a CD8+ cell.

1893. The method of Embodiment 1889, wherein an immune cell is a CD14+ cell.

1894. The method of Embodiment 1889, wherein an immune cell is a CD19+ cell.

1895. The method of Embodiment 1889, wherein an immune cell is a NK cell.

1896. The method of Embodiment 1889, wherein an immune cell is a Treg cell.

1897. The method of any one of Embodiments 1889-1896, wherein the cell is activated.

1898. The method of any one of Embodiments 1889-1896, wherein the cell is non-activated.

1899. The method of any one of Embodiments 1889-1898, wherein the oligonucleotide or composition targets and edits FAS, BID, CTLA4, PDCD1, CBLB, PTPN6, TRAC, or TRBC.

1900. A method for improving editing levels of an oligonucleotide, comprising incorporating a structural element recited in any one of the preceding Embodiments.

1901. A compound, oligonucleotide, composition, nucleobase, sugar, nucleoside, internucleotidic linkage, or method described in the present disclosure.

1902. An oligonucleotide, comprising a nucleobase as described herein.

1903. An oligonucleotide, comprising a sugar as described herein.

1904. An oligonucleotide, comprising an internucleotidic linkage as described herein.

1905. An oligonucleotide, comprising an internucleotidic linkage as described herein and a sugar which is bonded to the internucleotidic linkage as described herein (e.g., sm01n001).

EXEMPLIFICATION

[001114] Certain examples of provided technologies (compounds (oligonucleotides, reagents, etc.), compositions, methods (methods of preparation, use, assessment, etc.), etc.) were presented herein. Those skilled in the art appreciate that many technologies, e.g., those described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, WO 2021/071858, etc., can be utilized to prepare and/or assess properties and/or activities of provided technologies in accordance with the present disclosure.

[001115] Example 1. Useful technologies for assessing adenosine editing.

[001116] Oligonucleotide designs may be assessed using various systems. In some embodiments, cLuc oligonucleotides were prepared and assessed in HEK293T cells. In some embodiments, oligonucleotides targeting cLuc (Cypridina) were assessed in 293T cells transfected with plasmids for either human ADAR1 or human ADAR2 and a cLuc luciferase reporter plasmid. The cLuc reporter plasmid consisted of (Gaussia)gLuc-p2A-cLuc(W85X) with respect to luciferases. The cLuc reporter was activated by ADAR

mediated A>I editing. The editing activity of oligonucleotides was calculated using the equation:
Fold change = oligonucleotides treated (cLuc/gLuc) / mock (cLuc/gLuc)

[001117] In some embodiments, reporter plasmid and ADAR1 or ADAR2 plasmid were transfected together into HEK293T cells using the Lipofectamine 2000 transfection protocol (Thermo 11668030). After a suitable time period, e.g., 24 hours, the HEK293T cells expressing the reporter and ADAR plasmids were reverse transfected with the appropriate amount of oligonucleotides for each experiment. cLuc and gLuc activity was measured after 48, 72, and/or 96 hours using the Pierce™ Gaussia Luciferase Glow Assay Kit (Pierce™ 16161) or the Pierce™ Cypridina Luciferase Glow Assay Kit (Pierce™ 16170), respectively.

[001118] In some embodiments, oligonucleotides and compositions were assessed and confirmed to provide editing in various cells, e.g., mouse or human primary hepatocytes, primary human retinal pigment epithelial cells, cell lines, etc.. In some embodiments, oligonucleotide and compositions were assessed and confirmed to provide editing in subjects. In some embodiments, oligonucleotides and compositions were assessed and confirmed to provide editing in animals, e.g., mice, non-human primates (e.g., cynomolgus macaques), etc. In some embodiments, animals are transgenic animals, e.g., mice expressing human ADAR1. In some embodiments, animals are model animals comprising target adenosines associated with conditions, disorders or diseases, e.g., in many instances, G to A mutations. In some embodiments, provided technologies can provide efficient editing with or without exogenous ADAR polypeptides. In some embodiments, provided technologies can provide efficient editing without exogenous ADAR1 or ADAR2. In some embodiments, oligonucleotides and compositions are delivered by transfection (e.g., using transfection compositions such as Lipofectamine RNAimax). In some embodiments, oligonucleotides and compositions are delivered by gymnotic free update. Among other things, the present disclosure provides technologies for assessing agents, e.g., oligonucleotides, and compositions thereof, for editing, e.g., A to I (G) editing. In some embodiments, the present disclosure provides technologies that are useful for assessing agents (e.g., oligonucleotides) and compositions thereof that interact with, and/or modulate or utilize one or more functions of an ADAR polypeptide as described herein, e.g., an ADAR1 polypeptide. In some embodiments, the present disclosure provides non-human animal cells and/or non-human animals engineered to comprise and/or express an ADAR1 polypeptide or a characteristic portion thereof, or polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or comprises a primate ADAR1 or a characteristic portion thereof. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or comprises a primate ADAR1. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is a primate ADAR1. In some embodiments, a primate is a non-human primate. In some embodiments, a primate is human. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or comprises human p110 ADAR1 or a characteristic portion thereof. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or comprises human p110 ADAR1. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is human p110 ADAR1. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or

comprises human p150 ADAR1 or a characteristic portion thereof. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is or comprises human p150 ADAR1. In some embodiments, an ADAR1 polypeptide or a characteristic portion thereof is human p150 ADAR1. In some embodiments, a non-human animal is a rodent. In some embodiments, it is a rat. In some embodiments, it is a mouse. In some embodiments, the present disclosure provides mouse engineered to express human ADAR1. In some embodiments, the present disclosure provides mouse cells engineered to express human ADAR1.

[001119] Among other things, the present Example demonstrates that provided technologies are particularly useful for assessing agents, e.g., oligonucleotides, and compositions thereof that are useful for editing, e.g., adenosine editing described in the Examples. Among other things, the present disclosure provides and the present Example confirms that various agents (e.g., oligonucleotides) and compositions thereof that can provide editing in various human cells may show no or much lower levels of editing in certain cells (e.g., mouse cells) and certain animals such as rodents (e.g., mice) that do not contain or express human ADAR, e.g., human ADAR1; particularly, mice, a commonly used animal model, may be of limited uses for assessing various agents (e.g., oligonucleotides) for editing in humans, as agents active in human may show no or very low levels of activity. In some embodiments, the present disclosure provides cells and non-human animals (e.g., rodents such as mice) engineered to express human ADAR1 (e.g., human ADAR1 p110, p150, etc.), and their uses for assessing editing agents such as oligonucleotides and compositions thereof. Among other things, such engineered cells and/or animals can demonstrate activities that are more correlated with and/or predictive of activities in human cells than cells and/or animals not so engineered.

[001120] Generation of non-human mice expressing human ADAR1: Various technologies can be utilized in accordance with the present disclosure to provide mice engineered to express human ADAR1 polypeptide or a characteristic portion thereof. Certain useful technologies are described in the present disclosure and the priority applications, the entirety of each of which is independently incorporated by reference.

[001121] In some embodiments, in mouse cells and animals engineered to express human ADAR1, various oligonucleotides showed activity profiles that are much similar to their activity profiles in human cells compared to reference mouse cells and animals not engineered to express human ADAR1, for example, many oligonucleotides showed no or much lower levels of activity in reference mouse cells and animals not engineered to express human ADAR1 compared to human cells expressing human ADAR1 and/or mouse cells and animals engineered to express human ADAR1.

[001122] Various useful technologies for generating transgenic systems including animals are available to those skilled in the art and can be utilized in accordance with the present disclosure, including, etc., those described in the priority applications and WO 2021/071858, the entirety of each of which is incorporated herein by reference.

[001123] As described herein, animals engineered to comprise an ADAR1 polypeptide or a characteristic portion thereof, or to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof, may be crossed with various animals (e.g., model animals of

various conditions, disorders or diseases) to provide, among other things, animal models which comprise both characteristic elements associated with various conditions, disorders or diseases, and an ADAR1 polypeptide or a characteristic portion thereof or a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, an animal is a model animal comprising SERPINA1-Pi*Z. In some embodiments, an animal comprises 1024 G>A (E342K) mutation of human SERPINA1 and a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. Among other things, such animals are useful for assessing various agents, e.g., oligonucleotides, for editing 1024 G>A (E342K) mutation of human SERPINA1. Among other things, provided technologies, *e.g.,* non-human animals engineered to comprise or express ADAR1 polypeptide or a characteristic portion thereof, are particularly useful for assessing agents for adenosine editing.

[001124] In some embodiments, a huADAR mouse as described herein is crossed with another mouse comprising a nucleotide sequence of interest (e.g., a mutation associated with a condition, disorder or disease). In certain embodiments, such a cross is performed using *in vitro* fertilization as is known in the art in accordance with the present disclosure. In certain embodiments, such a mouse comprises a human serpin family A member 1 (SERPINA1) polynucleotide sequence or a characteristic portion thereof. In certain embodiments, such a mouse is a SERPINA1-Pi*Z mouse, comprising a human SERPINA1 gene comprising a G to A mutation that corresponds to a 1024 G>A (E342K) mutation. In some embodiments, resultant offspring comprise both a human SERPINA1-Pi*Z polynucleotide sequence or a characteristic portion thereof (e.g., a portion comprising a mutation, e.g., 1024 G>A associated with a condition, disorder or disease) and a huADAR1 polynucleotide sequence or a fragment thereof. In some embodiments, double transgenic animals (e.g., comprising a human ADAR1 sequence or a characteristic portion thereof and a sequence associated with a condition, disorder or disease) may also comprise additional background mutations or alleles in heterozygous, hemizygous, and/or homozygous form that render them humanized (i.e. with immunodeficient phenotypes), such genotypes include but are not limited to NOD.Cg-*Prkdc*^{scid} *Il2rgtm1*^{Wjl}/SzJ, or NOD/ShiLtJ, alternative suitable humanized mouse strains are known in the art. In some embodiments, a mouse comprising a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof is crossed with a mouse comprising a SERPINA1 mutation (e.g., 1024 G>A associated with a condition, disorder or disease (e.g., alpha 1-antitrypsin (A1AT) deficiency)). In some embodiments, a second mouse crossed with is The Jackson Laboratory Stock No: 028842; NSG-PiZ (see also Borel F; Tang Q; Gernoux G; Greer C; Wang Z; Barzel A; Kay MA; Shultz LD; Greiner DL; Flotte TR; Brehm MA; Mueller C. 2017. Survival Advantage of Both Human Hepatocyte Xenografts and Genome-Edited Hepatocytes for Treatment of alpha-1 Antitrypsin Deficiency. Mol Ther 25(11):2477-2489PubMed: 29032169MGI: J:243726, and Li S; Ling C; Zhong L; Li M; Su Q; He R; Tang Q; Greiner DL; Shultz LD; Brehm MA; Flotte TR; Mueller C; Srivastava A; Gao G. 2015. Efficient and Targeted Transduction of Nonhuman Primate Liver With Systemically Delivered Optimized AAV3B Vectors. Mol Ther 23(12):1867-76PubMed: 26403887MGI: J:230567). As described herein, in some embodiments, a huADAR mouse is engineered to comprise and/or express a polynucleotide whose sequence

encodes a human ADAR1 p110 polypeptide or a characteristic portion thereof. In some embodiments, a huADAR mouse is engineered to comprise and/or express a polynucleotide whose sequence encodes a human ADAR1 p150 polypeptide or a characteristic portion thereof.

[001125] In some embodiments, a huADAR mouse as described herein was crossed with another mouse comprising a nucleotide sequence of interest. In some embodiments, a mouse comprising a polynucleotide whose sequence encoded an ADAR1 polypeptide was crossed with a mouse comprising a SERPINA1 mutation (e.g., 1024 G>A associated with a condition, disorder or disease (e.g., alpha 1-antitrypsin (A1AT) deficiency)). In some embodiments, such a cross was performed using *in vitro* fertilization as is known in the art in accordance with the present disclosure. In some embodiments, such a mouse comprised a human serpin family A member 1 (SERPINA1) polynucleotide sequence or a characteristic portion thereof. In some embodiments, such a mouse was a SERPINA1-Pi*Z mouse, comprising a human SERPINA1 gene comprising a G to A mutation that corresponds to, e.g., a 1024 G>A (E342K) mutation, or a genetic feature corresponding thereto. In some embodiments, resultant offspring comprised both a human SERPINA1-Pi*Z polynucleotide sequence and a huADAR1 polynucleotide sequence. In some embodiments, double transgenic animals also comprised additional background mutations or alleles in heterozygous, hemizygous, and/or homozygous (wild type or mutant) form, that in mutant form render them humanized (e.g., with immunodeficient phenotypes). In some embodiments, such genotypes included NOD.Cg-*Prkdc*^{scid} *Il2rgtm1*^{Wjl}/SzJ.

[001126] As appreciated by those skilled in the art, various technologies may be utilized for cross breeding in accordance with the present disclosure. In some embodiments, a technology is or comprises IVF (e.g., using sperms of a heterozygous or homozygous huADAR mouse and oocytes from another mouse, or vice versa). In some embodiments, a technology is or comprises natural breeding (e.g., using sperms of a heterozygous or homozygous huADAR mouse and oocytes from another mouse, or vice versa).

[001127] For example, in some embodiments, heterozygous sperms from a huADAR male mice and oocytes from NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ (NSG-PiZ, Stock #028842) female mice are utilized via, e.g., IVF, to generate Prkdcscid heterozygous / Il2rgtm1Wjl heterozygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous female mice and Prkdcscid heterozygous / Il2rgtm1Wjl hemizygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous male mice. In some embodiments, homozygous sperms from a huADAR male mice and oocytes from NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ (NSG-PiZ, Stock #028842) female mice are utilized via, e.g., IVF, to generate Prkdcscid heterozygous / Il2rgtm1Wjl heterozygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous female mice and Prkdcscid heterozygous / Il2rgtm1Wjl hemizygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous male mice. In some embodiments, homozygous sperm from strain "hADAR" male mice and oocytes from NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ (NSG-PiZ, Stock #028842) female mice are utilized, and resulting mice are crossed to, e.g., NOD/ShiLtJ (The Jackson Laboratory Stock #001976) mice to establish a series of colonies. In some embodiments, generated mice are (assuming the Prkdcscid / Il2rgtm1Wjl /

Tg(SERPINA1*E342K)#Slcw / hADAR gene order) HET HET HET HET, HET WILD HET HET, WILD HET HET HET, WILD WILD HET HET, HET HEMI HET HET, HET HEMI HET WILD, HET HET HET WILD, and/or WILD HEMI HET HET. One skilled in the art appreciates that male or female gametes may be donated from either strain *e.g.,* that in some embodiments oocytes may be donated from huADAR lines, while sperm may be donated from the other genotype, e.g., NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl} Tg(SERPINA1*E342K)#Slcw/SzJ (NSG-PiZ, Stock #028842). In some embodiments, a huADAR (or hADAR) mice is engineered to comprise and/or express a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof. In some embodiments, an animal comprises a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof in its genome. In some embodiments, an animal comprises a polynucleotide whose sequence encodes an ADAR1 polypeptide or a characteristic portion thereof in its germline genome. In some embodiments, an ADAR1 polypeptide is human ADAR1. In some embodiments, a human ADAR1 is human ADAR1 p110. In some embodiments, a human ADAR1 is human ADAR1 p150. As examples, a number of animals comprising human ADAR1 p110 and 1024 G>A (E342K) mutation in human SERPINA1 were generated using one or more protocols described herein (e.g., using heterozygous hADAR1 sperms and IVF). As appreciated by those skilled in the art, in some embodiments, generated animals can be further bred to produce animals of desired genotypes, e.g., heterozygous, hemizygous, or homozygous mice. In some embodiments, using IVF, heterozygous sperms from huADAR male mice and oocytes from NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ (NSG-PiZ, Stock #028842) female mice were crossed to generate Prkdcscid heterozygous / Il2rgtm1Wjl heterozygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous female mice and Prkdcscid heterozygous / Il2rgtm1Wjl hemizygous / Tg(SERPINA1*E342K)#Slcw heterozygous / hADAR heterozygous male mice. Additionally, pups were produced with genotypes (assuming the Prkdcscid / Il2rgtm1Wjl / Tg(SERPINA1*E342K)#Slcw / hADAR gene order) HET HET HET HET, HET WILD HET HET, WILD HET HET HET, WILD WILD HET HET, HET HEMI HET HET, HET HEMI HET WILD, HET HET HET WILD, and/or WILD HEMI HET HET. A number of animals comprising human ADAR1 p110 and 1024 G>A (E342K) mutation in human SERPINA1 were generated using one or more protocols described herein (e.g., using heterozygous hADAR1 sperms and IVF).

[001128] In some embodiments, provided technologies, e.g., oligonucleotides and compositions thereof, are assessed in such animal models. In some embodiments, levels, properties, and/or activities of desired products (e.g., properly folded wild-type A1AT protein in serum) are increased, and/or levels, properties, and/or activities of undesired products (e.g., mutant (e.g., E342K) A1AT protein in serum) are decreased, in observed amounts (e.g., ng/mL in serum) and/or relatively (e.g., as % of total proteins or total A1AT proteins).

[001129] Provided technologies can provide activities, e.g., adenosine editing, in various types of cells, tissues, organs, organisms, etc. (e.g., liver, kidney, CNS, neuronal cells, astrocytes, hepatocytes, etc.). In some embodiments, editing was confirmed in immune cells, e.g., CD8+ T-cells (in some instances pre-stimulated

with cytokines for, e.g., 24 or 96 hrs). In some embodiments, editing was confirmed in fibroblast cell lines. In some embodiments, editing was confirmed in NHP eyes (retina) ex-vivo. Editing of target adenosines in various target transcripts were observed, confirming that provided technologies are generally applicable. Certain target transcripts were described herein and in, e.g., the priority applications and WO 2021/071858.

[001130] Oligonucleotides and compositions can be delivered utilizing many technologies in accordance with the present disclosure. For example, in some embodiments, they were delivered by transfection. In some embodiments, they were delivered by gymnotic uptake. In some embodiments, oligonucleotides comprise moieties that can facilitate delivery. For example, in some embodiments, a moiety is a ligand for a polypeptide, e.g., a receptor, in many instances, on cell surface. In some embodiments, a polypeptide is expressed at a higher level by a type or population of cells, a tissue, etc. so that it may be utilized for delivery. In some embodiments, a ligand is an ASGPR ligand. In some embodiments, a ligand is or comprises GalNAc or a derivative thereof. In some embodiments, an oligonucleotide may comprise two or more ligand moieties, each of which is independently a ligand of a polypeptide. In some embodiments, an oligonucleotide comprises two or more copies of a ligand moiety. In some embodiments, a moiety targets one or more characteristics (e.g., pH, redox, etc.) of a location or environment.

[001131] In some embodiments, technologies of the provided technology can provide increased stability, high levels of editing, etc. In some embodiments, provided technologies can provide desired editing activities for a long period of time, e.g., about or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or more days, after a last dose. In some embodiments, desired editing activities/levels of editing may be maintained for a long period of time, e.g., about or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or more days, after a last dose.

[001132] In some embodiments, provided technologies can provide high levels of selectivity. In some embodiments, about or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% observed adenosine editing are at target adenosines. In some embodiments, about or at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% observed adenosine editing in coding regions are at target adenosines. In some embodiments, about or at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% observed adenosine editing in target nucleic acids (e.g., transcripts of target genes) are at target adenosines. In some embodiments, about or at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% observed adenosine editing in coding regions of target nucleic acids (e.g., transcripts of target genes) are at target adenosines. Various technologies, e.g., RNA-Seq, are available to those skilled in the art to assess selectivity; certain such technologies are described herein or in the priority applications or WO 2021/071858, the entirety of each of which is independently incorporated herein by reference. In some embodiments, a percentage for a selectivity described herein is at least about 80%. In some embodiments, it is at least about 85%. In some embodiments, it is at least about 90%. In some embodiments, it is at least about 95%. In some embodiments, it is at least about 96%. In some embodiments, it is at least about 97%. In some embodiments, it is at least about 98%. In some embodiments, it is at least about 99%. In some embodiments, it is at least

about 99.5%. In some embodiments, it is at least about 99.9%. In some embodiments, it is about 100%. In some embodiments, no off-target editing is observed. In some embodiments, provided technology provides high selectivity *in vivo*.

[001133] In some embodiments, the present disclosure provides multiplex editing. In some embodiments, multiple target adenosines are edited together, one or more or each of which is independently edited at a comparable level compared to when edited individually.

[001134] Various results are presented in, e.g., Figures and Tables herein, as examples illustrating various benefits and advantages provided technologies can provide.

[001135] As demonstrated herein, the present disclosure among other things provide oligonucleotides comprising various modifications (e.g., nucleobase modifications, sugar modifications, linkage modifications, etc., and combinations and patterns thereof) that can provide efficient editing.

[001136] In some embodiments, utilization of certain sugars, e.g., natural DNA sugars, 2'-F modified sugars, etc. at and/or near editing sites provide editing activities. In some embodiments, an oligonucleotide comprises 5'-$N_1N_0N_{-1}$–3', wherein each of N_1, N_0, and N_{-1} is independently a nucleoside, N_1 and N_0 bond to an internucleotidic linkage as described herein, and N_{-1} and N_0 bond to an internucleotidic linkage as described herein, and N_0 is opposite to a target adenosine. In some embodiments, the sugar of each of N_1, N_0, and N_{-1} is independently a natural DNA sugar. In some embodiments, the sugar of N_1 is a 2'-modified sugar (e.g., a 2'-F modified sugar), and the sugar of each of N_0 and N_{-1} is independently a natural DNA sugar. In some embodiments, such oligonucleotides provide high editing levels. In some embodiments, 2'-OR modified sugars (wherein R is not –H) are utilized outside of a second subdomain or editing region, e.g., in a first domain, a first subdomain, and/or a third subdomain. Such modified sugars can be utilized at various positions in these domains/subdomains and are well tolerated and in various instances can improve properties and/or activities of oligonucleotides.

[001137] As demonstrated herein, provided technologies can provide efficient editing using significantly shorter oligonucleotides compared to various prior reported technologies. In some embodiments, oligonucleotides of various lengths, e.g., 27, 28, 29, 20, 31, 32, or more, nucleosides can provide editing.

[001138] In some embodiments, base sequences of oligonucleotides are of sufficient complementarity to those of target nucleic acids so that oligonucleotides can form duplexes under suitable conditions, e.g., *in vivo* or *in vitro* editing conditions. In some embodiments, oligonucleotides selectively form duplexes with target nucleic acids over non-target nucleic acids. While certain levels of complementarity to target nucleic acids are preferred or required for various uses including target adenosine editing, full complementarity is generally not required. In some embodiments, there are one or mismatches, bulges, etc. as described herein. In some embodiments, the nucleobase of a nucleoside opposite to target adenosine, N_0, is not complementary to a target adenosine. In some embodiments, hypoxanthine is utilized in place of G particularly if close or next to N_0. In some embodiments, first domains, first subdomains and/or third subdomains comprise one or more, e.g., 1, 2, 3, 4, or more, mismatches.

[001139] In some embodiments, oligonucleotides are provided in chirally controlled oligonucleotide compositions. In some embodiments, as illustrated herein, chirally controlled oligonucleotide compositions provide various desired properties and/or activities. In some embodiments, chirally controlled oligonucleotide compositions provide improved properties and/or activities compared to corresponding stereorandom oligonucleotide compositions (e.g., of oligonucleotides of the same constitution but not chirally controlled at chiral linkage phosphorus).

[001140] Among other things, Applicant has confirmed that compositions of oligonucleotides comprising various modifications can provide target editing, and nucleosides opposite to target adenosines can be placed at various locations in oligonucleotides (e.g., in some cases, positions 5, 6, 7, 8, 9 or more from the 3'-end). Also confirmed is that different versions of GalNAc (e.g., in Mod001 or L025) can be utilized to provide delivery and/or activities. As appreciate by those skilled in the art and described and confirmed herein, after editing edited nucleobases may perform various functions of G (and in some instances, editing may be referred to as A to G). In various embodiments, natural RNA sugars may be utilized in provided oligonucleotides, and in some cases, in nucleosides opposite to target adenosines. In some embodiments, RNA or DNA nucleosides are utilized at 3' immediate position (N_{-1}) and have hypoxanthine as their nucleobase. In some embodiments, a 3' immediate I or dI nucleoside is bonded to its 3' immediate nucleoside through *Sp* non-negatively charged internucleotidic linkages such as phosphoryl guanidine internucleotidic linkage like n001. Among other things, it was confirmed that various number of non-negatively charged internucleotidic linkages may be utilized at various portions in accordance with the present disclosure. In some embodiments, non-complementary base pairing (e.g., wobbles and/or mismatches) is utilized in addition to an editing region or a second subdomain. In some embodiments, it was confirmed that removing non-complementary base pairing (e.g., wobbles and/or mismatches) may improve editing efficiency. In some embodiments, certain nucleobases were observed to provide improved properties and/or activities. Among other things, it was confirmed that in some embodiments oligonucleotides comprising various modified nucleobases (or abasic nucleoside), at N_0, can provide editing. In some embodiments, it was observed that oligonucleotides comprising certain base modifications, such as b001A, b002A, b008U, etc., increased editing activity when compared to a reference composition. In some embodiments, it was observed that oligonucleotides comprising certain base modifications, such as b001A, b002A, b008U, etc., at N_0, increased editing activity when compared to a reference composition. In some embodiments, provided oligonucleotides comprise abasic moieties between nucleosides comprising nucleobases. Various oligonucleotides comprising one or more abasic units in place of nucleosides comprising nucleobases were assessed and confirmed to be able to provide editing activities. In some embodiments, it was observed that abasic units at certain positions provided higher activities than other positions. In some embodiments, it was observed that oligonucleotides may provide different absolute and/or relative editing levels with ADAR1-p110, ADAR1-p150 and ADAR2 in certain circumstances.

[001141] In some embodiments, an oligonucleotide is fully complementary to a sequence of the same length in a target nucleic acid.

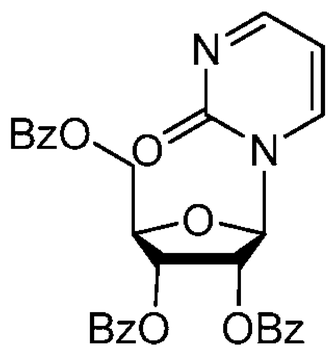
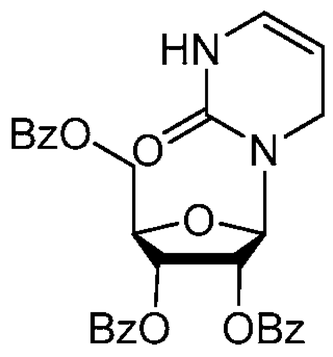
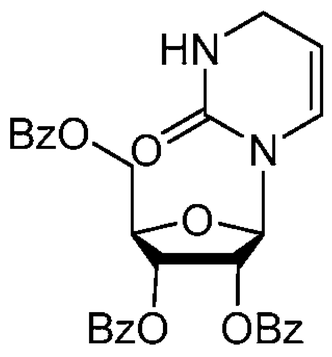
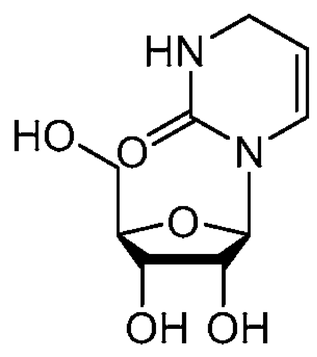
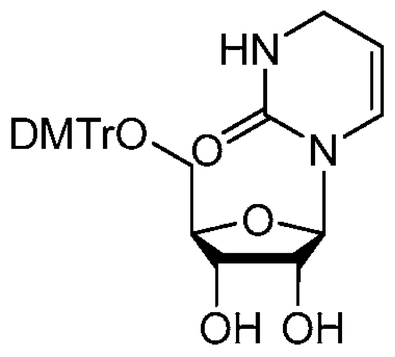
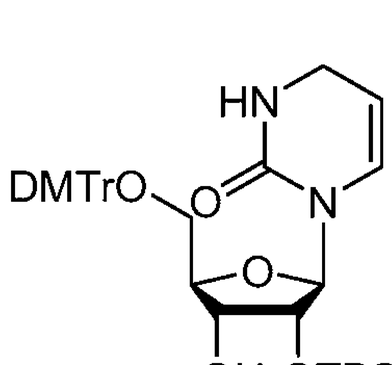
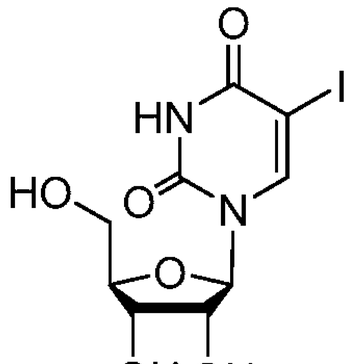
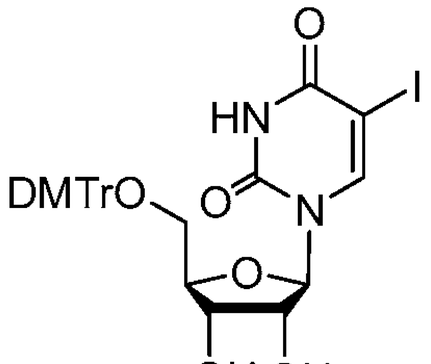
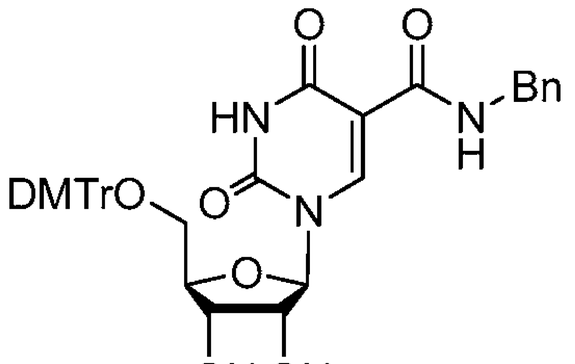
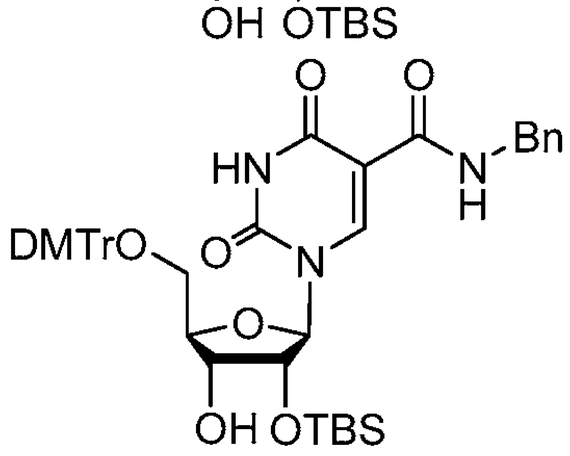
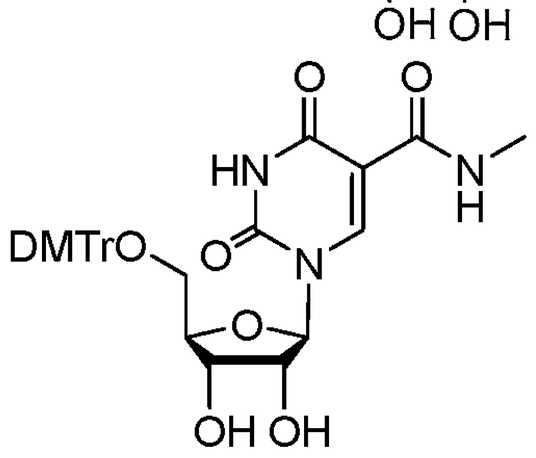
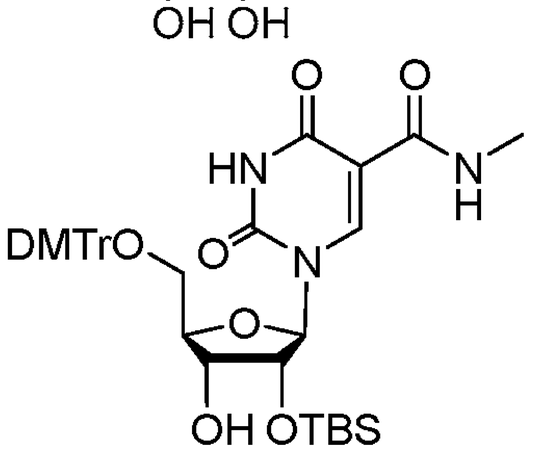
[001142] Provided technologies can provide robust editing in the presence of ADAR1 and/or ADAR2. Provided technologies can provide robust editing in the presence of ADAR1-p110 and/or ADAR1-p150.

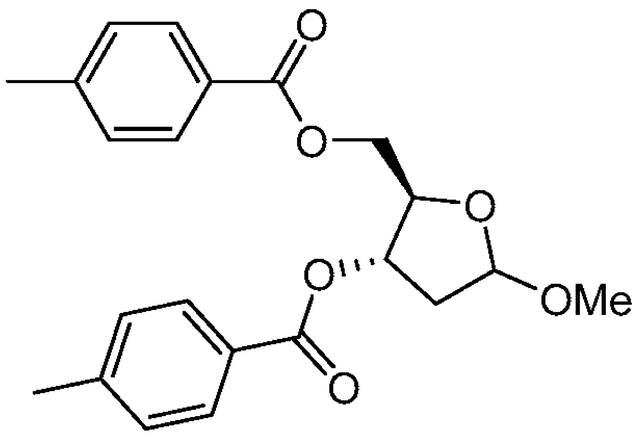
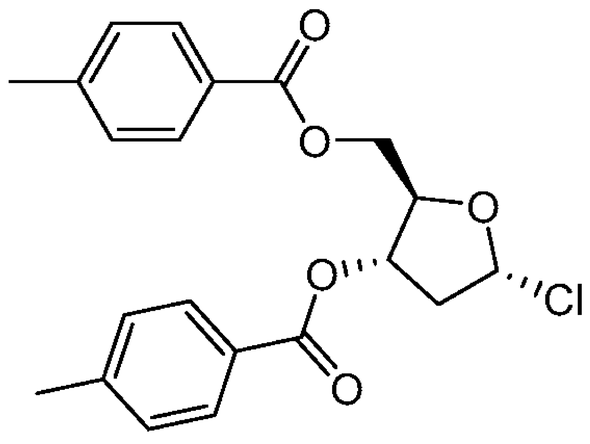
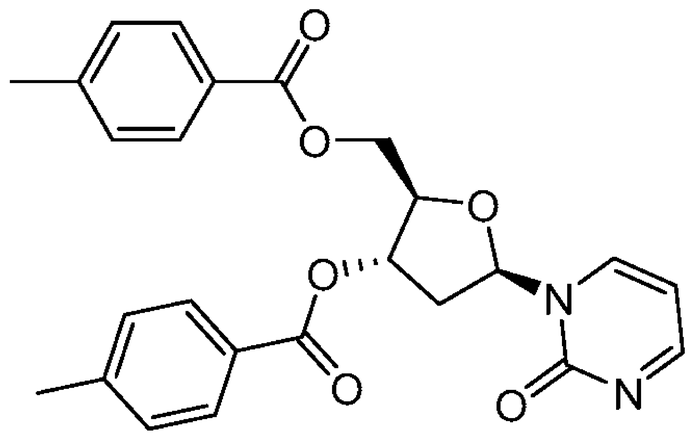
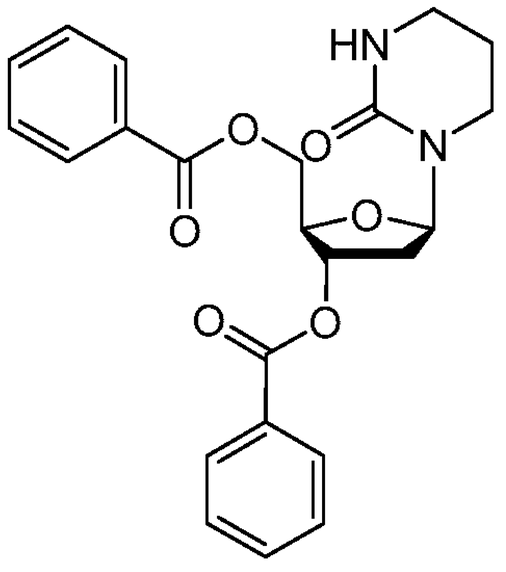
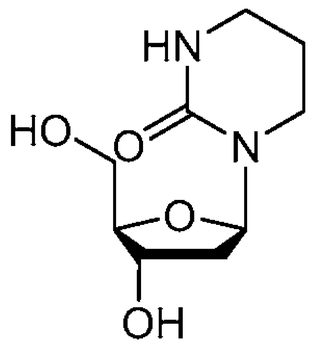
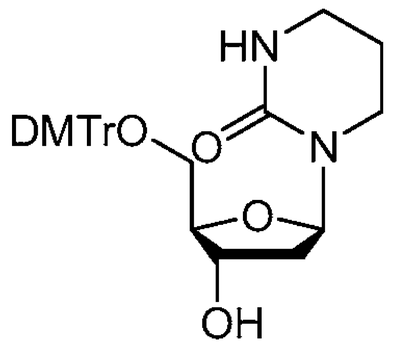
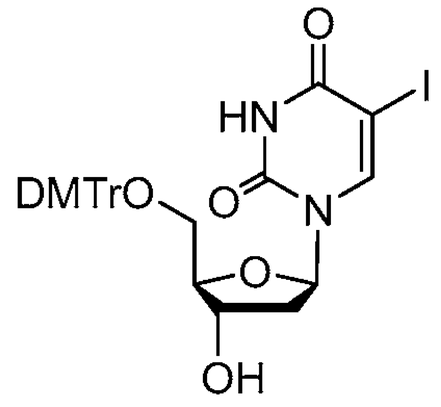
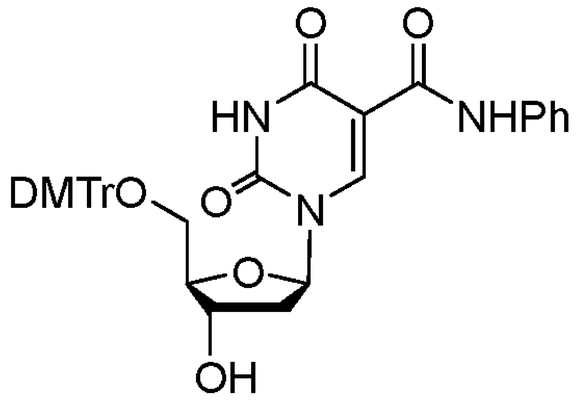
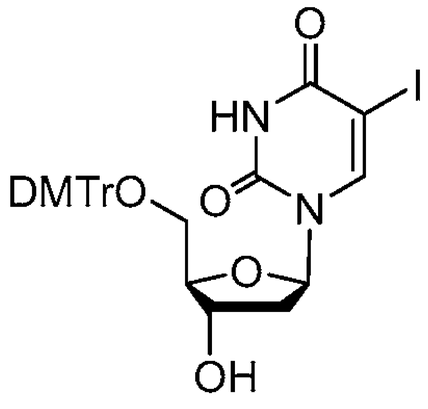
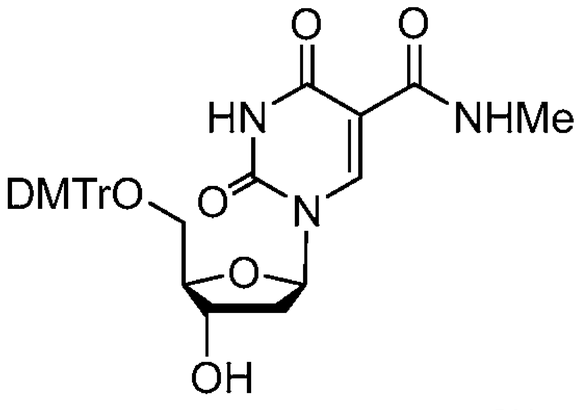
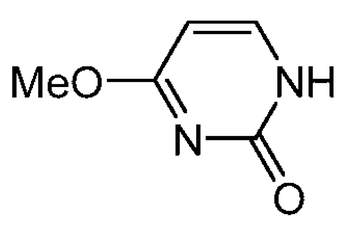
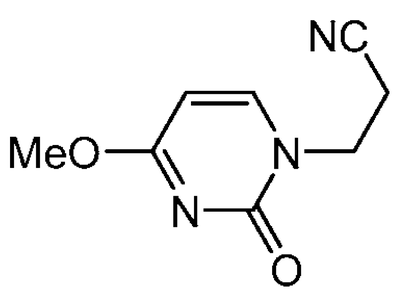
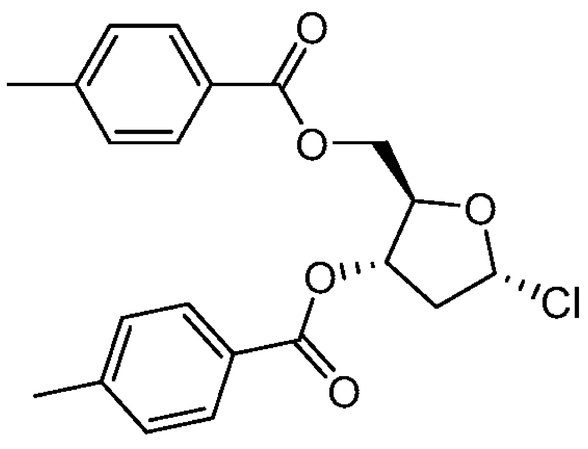
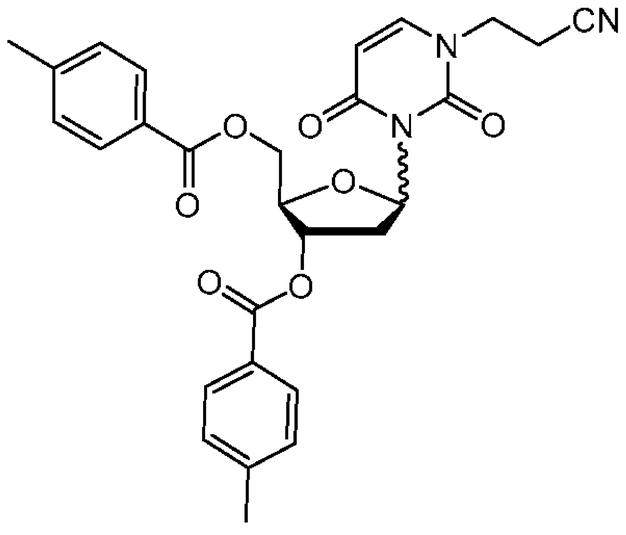
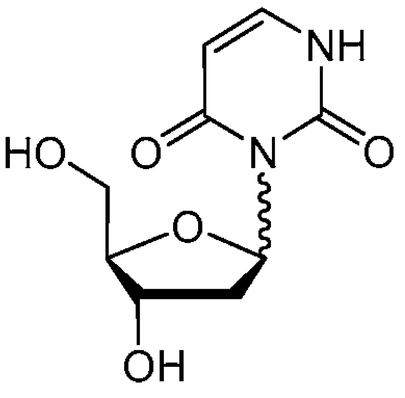
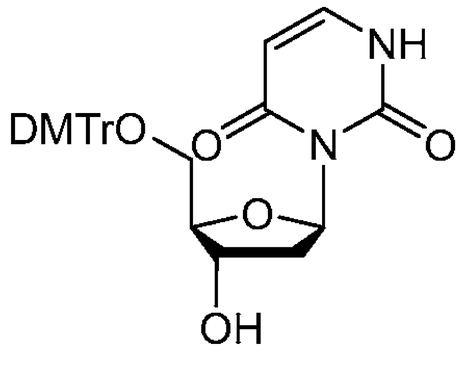
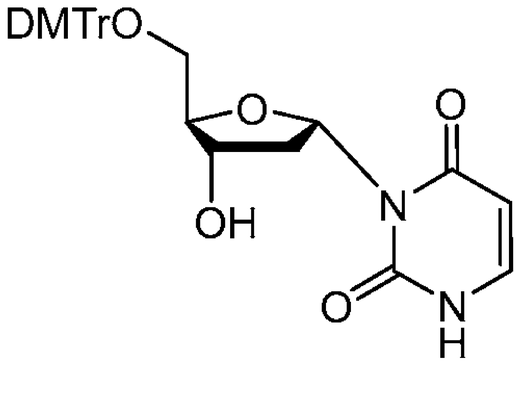
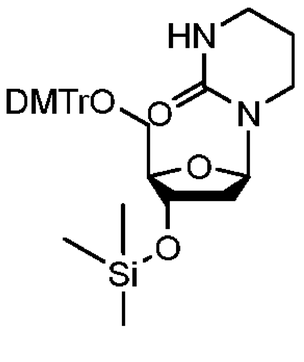
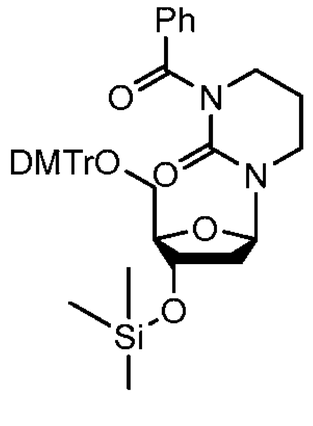
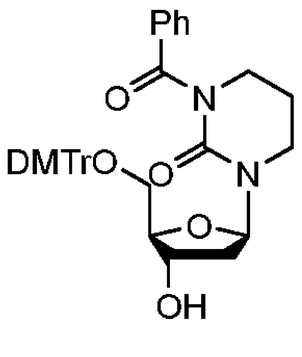
[001143] Data confirming various properties, activities, advantages, etc. of technologies of the present disclosure are provided as examples in various examples and figures including those in the priority applications, the entirety of each of which is independently incorporated herein by reference. Certain useful technologies, e.g., structural elements, assays, targets, etc., that can be utilized in accordance with the present disclosure are described in WO 2021/071858, the entirety of which is incorporated herein by reference.

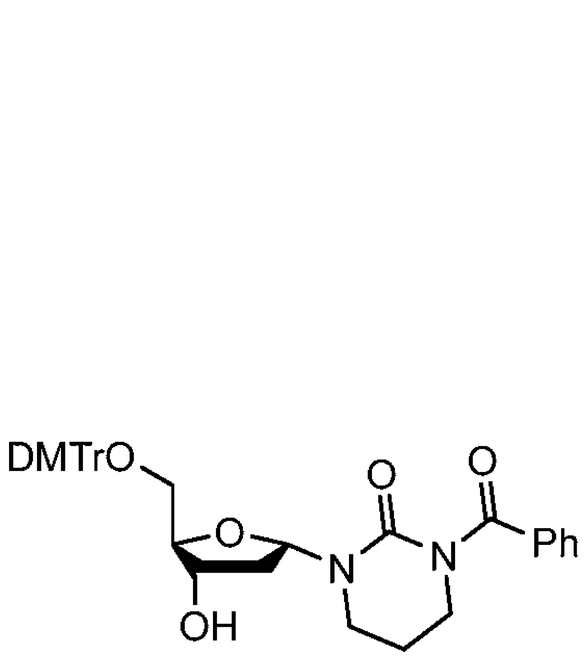
[001144] Example 2. Technologies for preparing oligonucleotide and compositions.

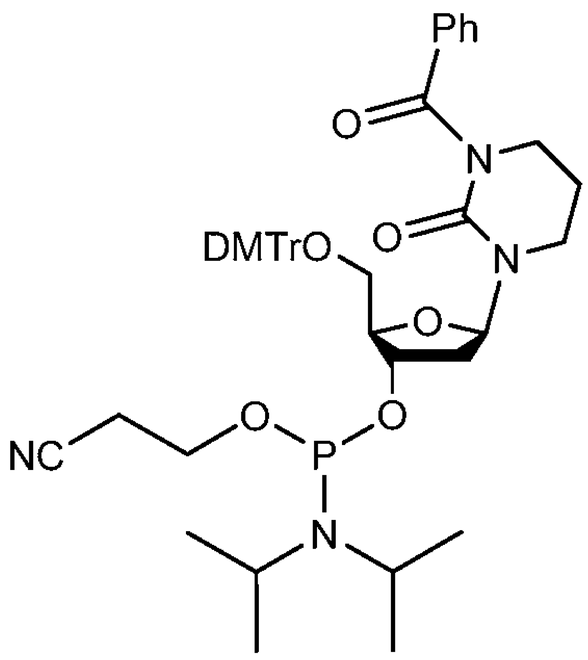
[001145] Various technologies (e.g., phosphoramidites, nucleobases, nucleosides, etc.) for preparing provided technologies (e.g., oligonucleotides, compositions (e.g., oligonucleotide compositions, pharmaceutical compositions, etc.), etc.) can be utilized in accordance with the present disclosure, including, for example, methods and reagents described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the methods and reagents of each of which are incorporated herein by reference. In some embodiments, the present disclosure provides useful technologies for preparing oligonucleotides and compositions thereof.

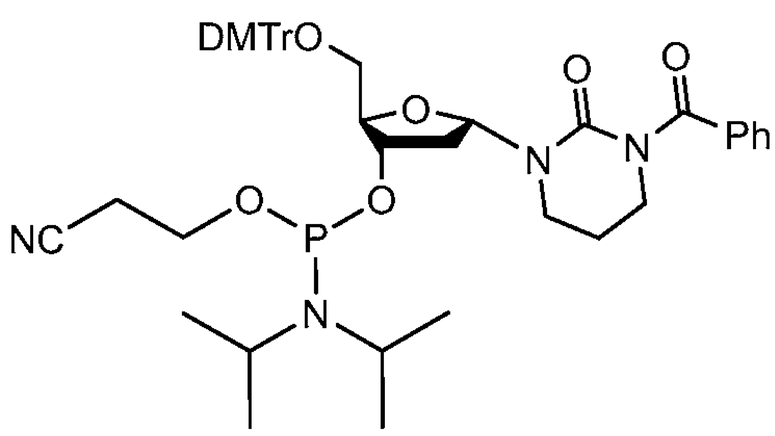
[001146] In some embodiments, useful compounds including those described below or salts thereof. In some embodiments, compounds were prepared utilizing technologies described in the priority applications and WO 2021/071858, the entirety of each of which is incorporated herein by reference.

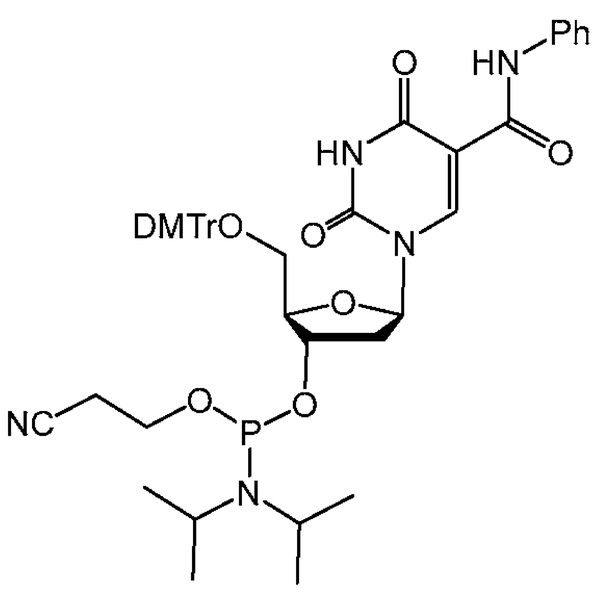













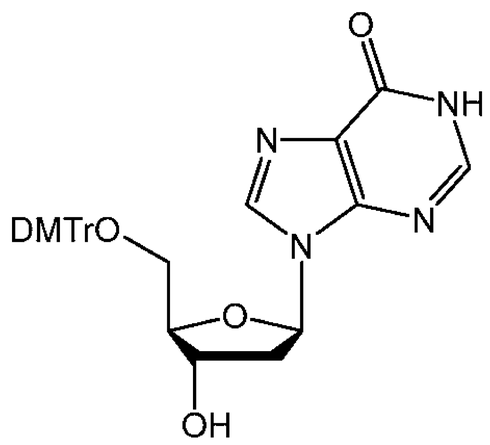





















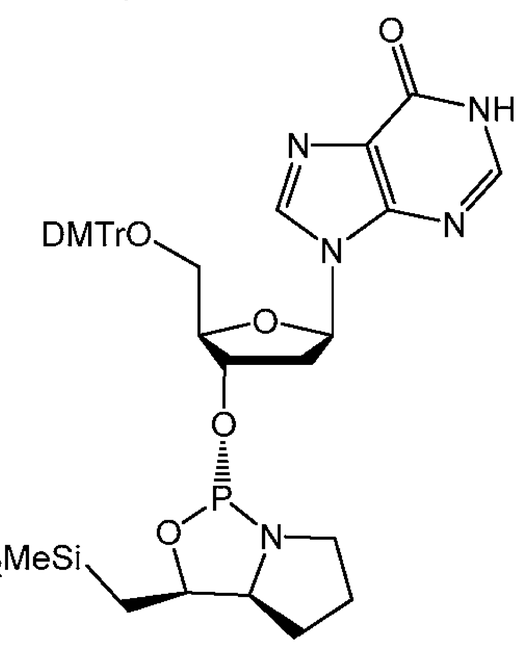


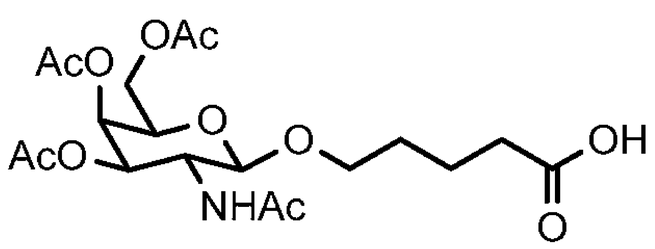


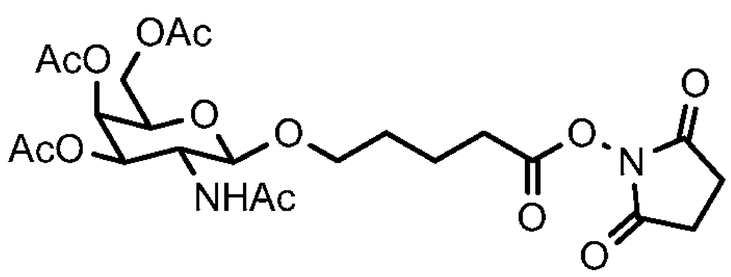


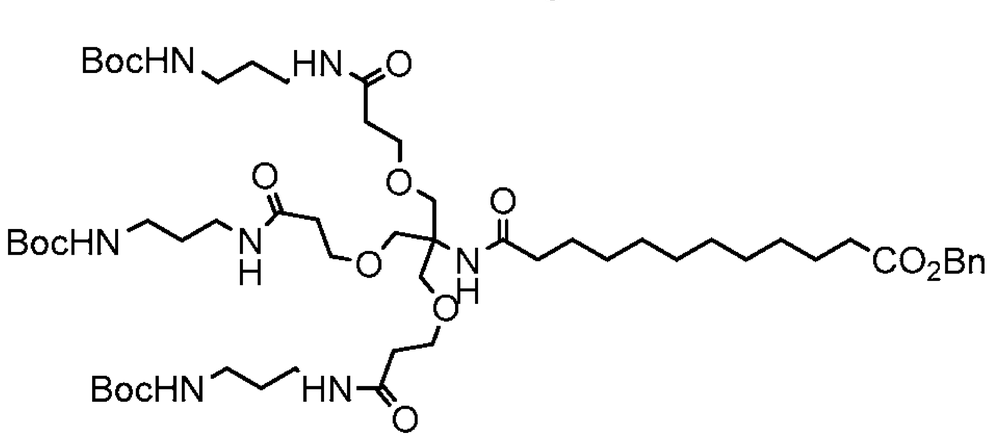


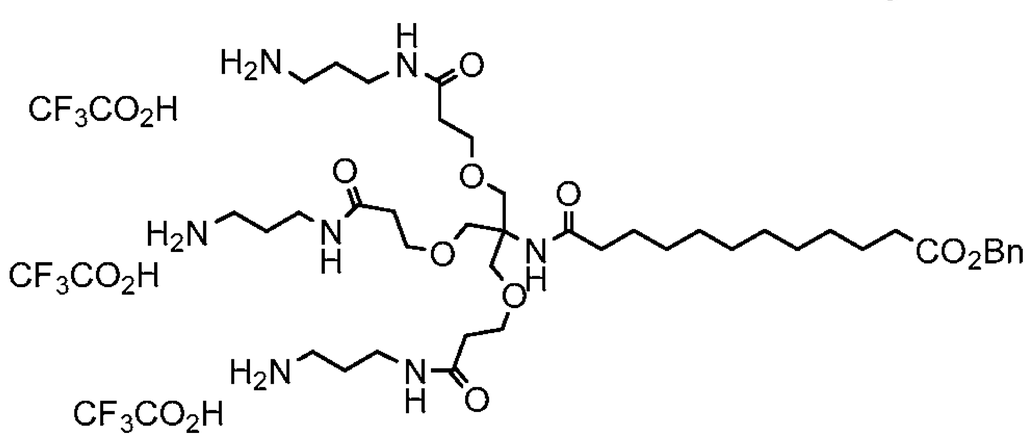


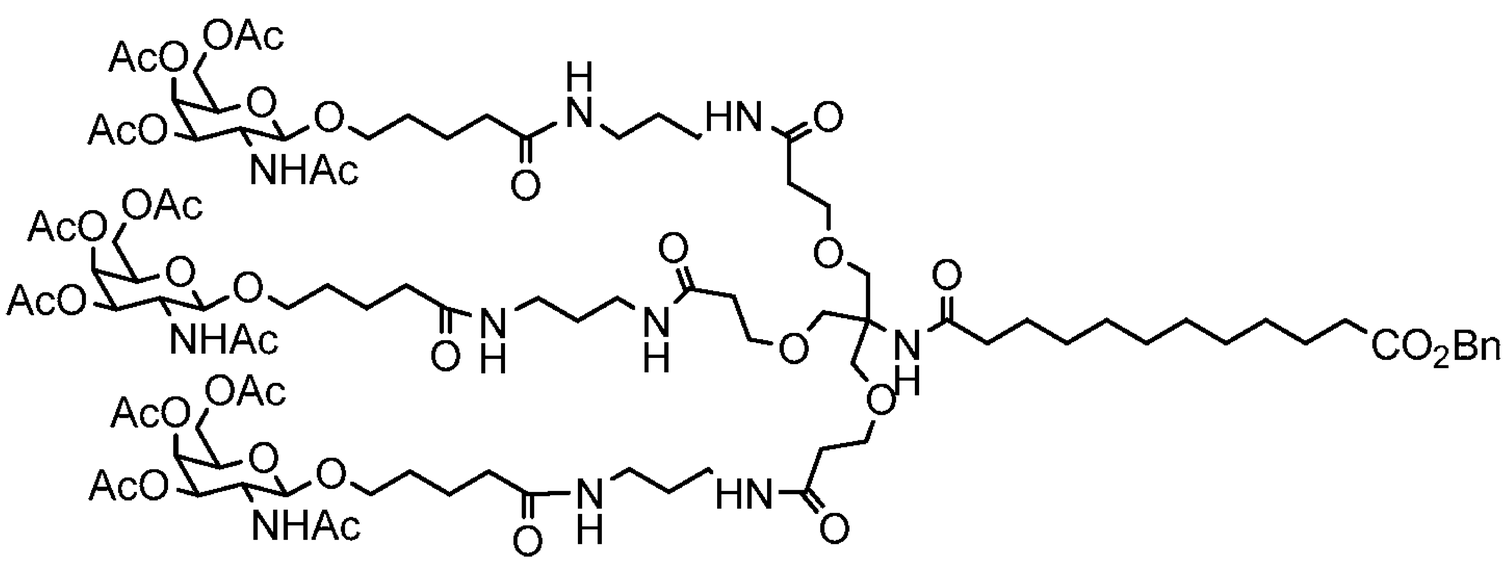


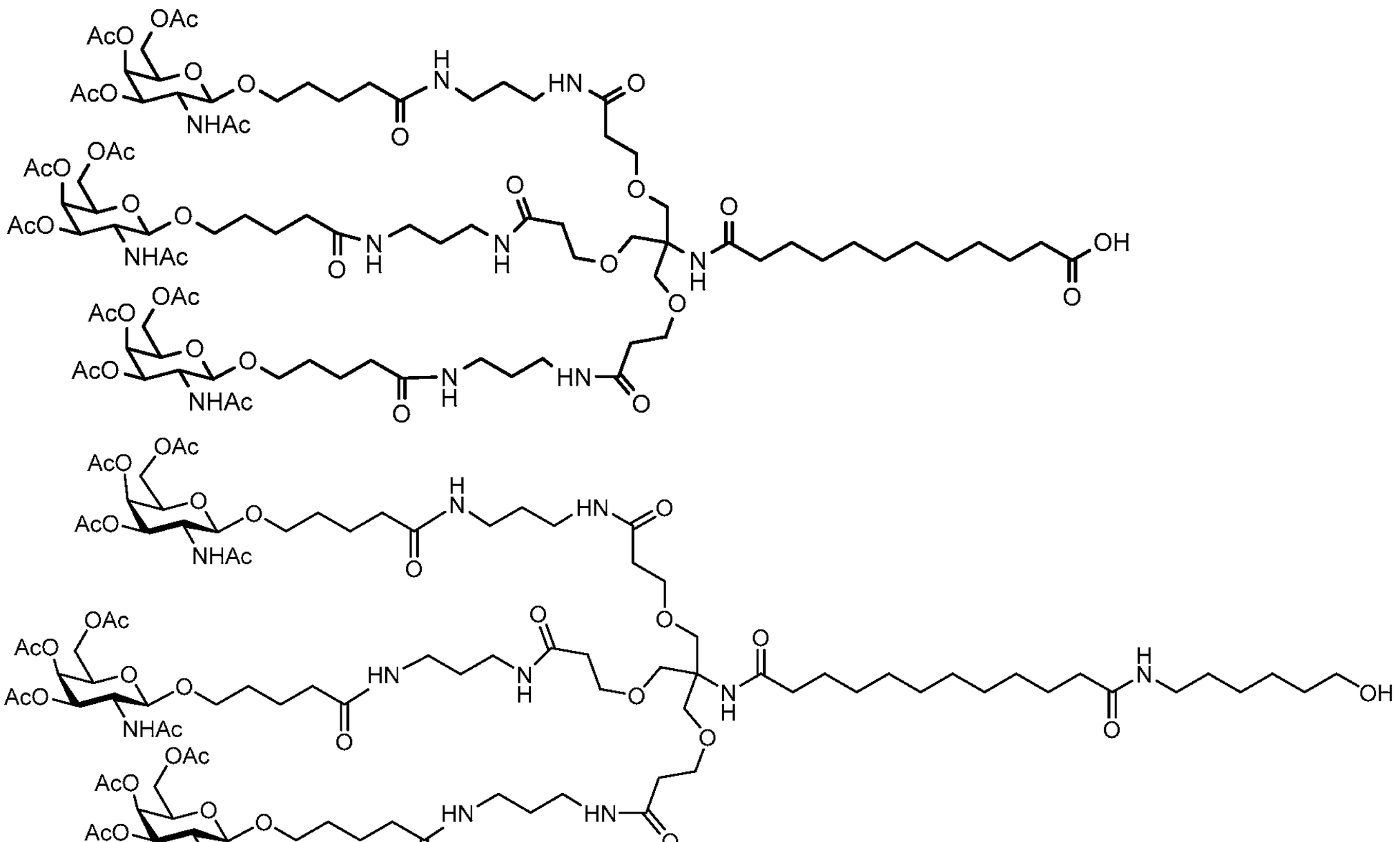


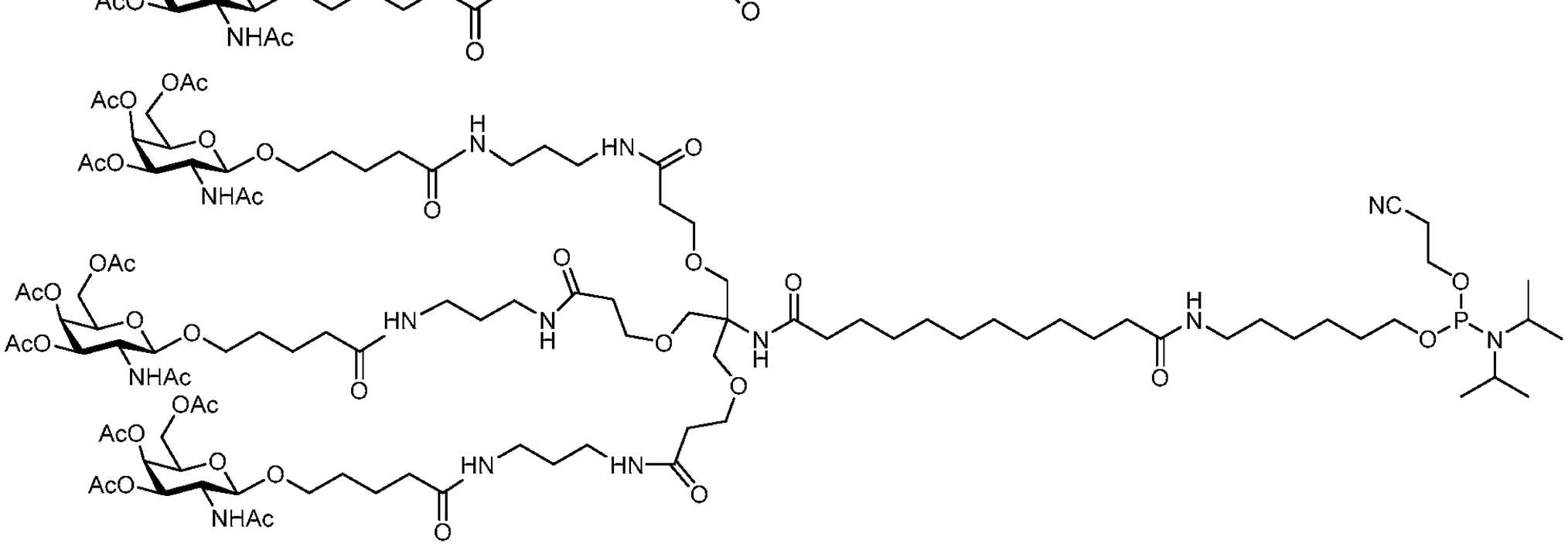


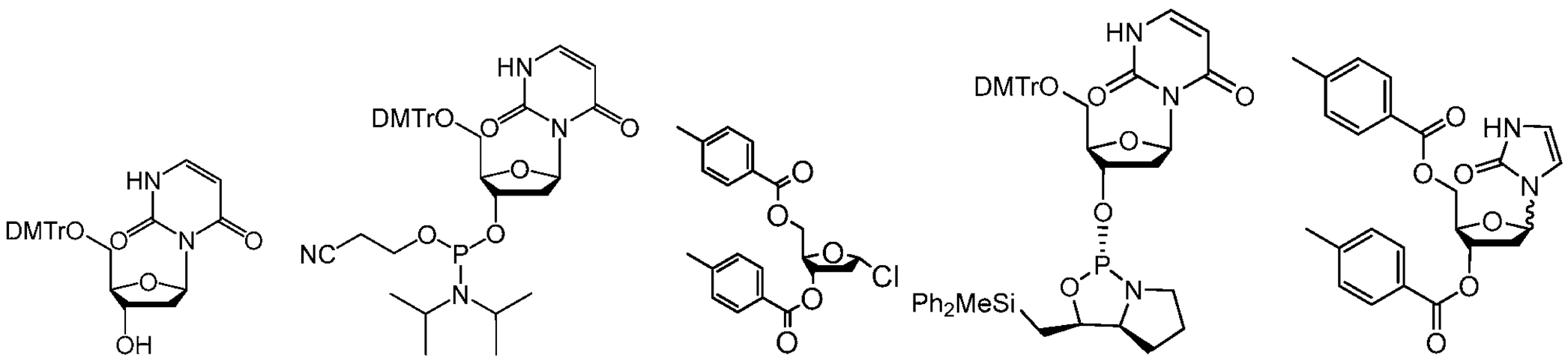


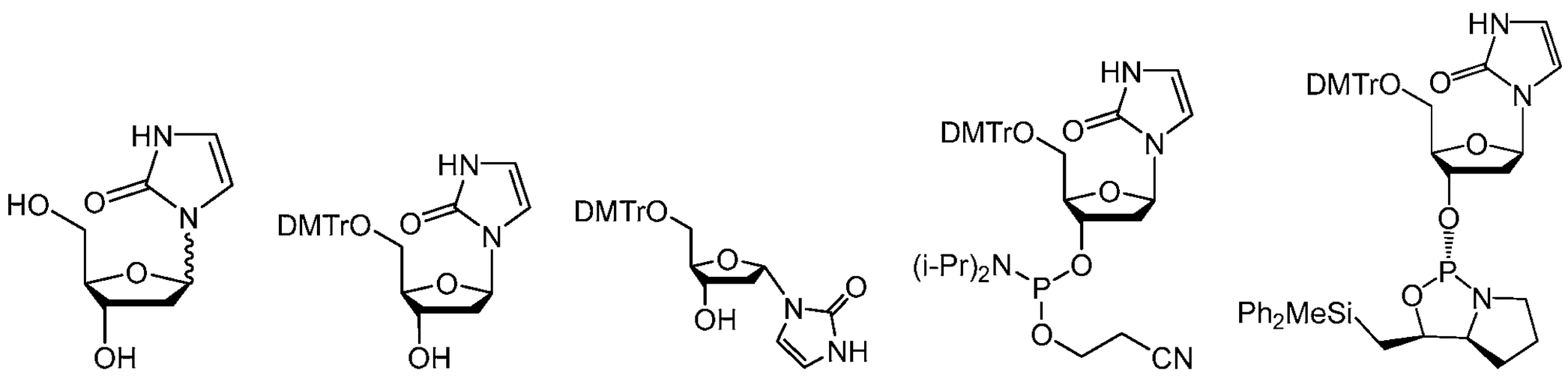


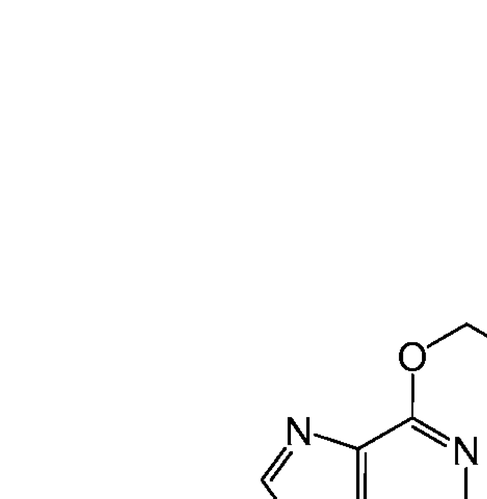


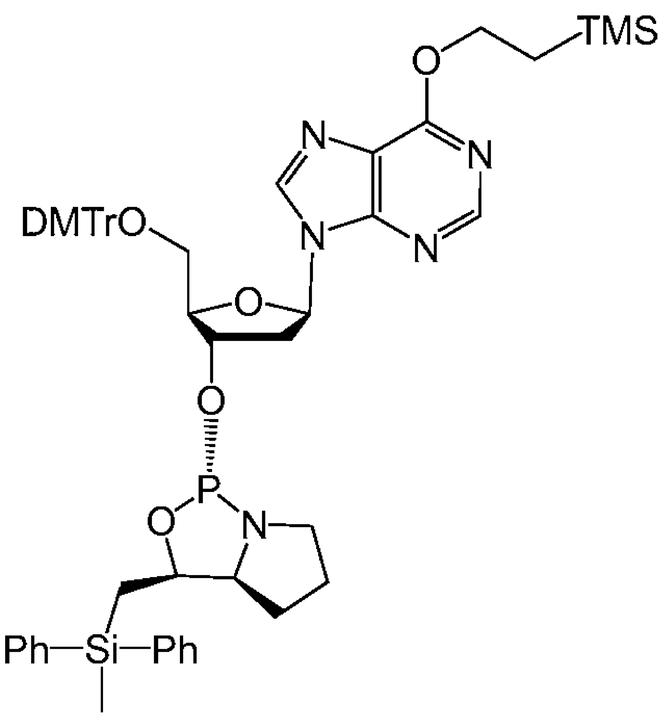


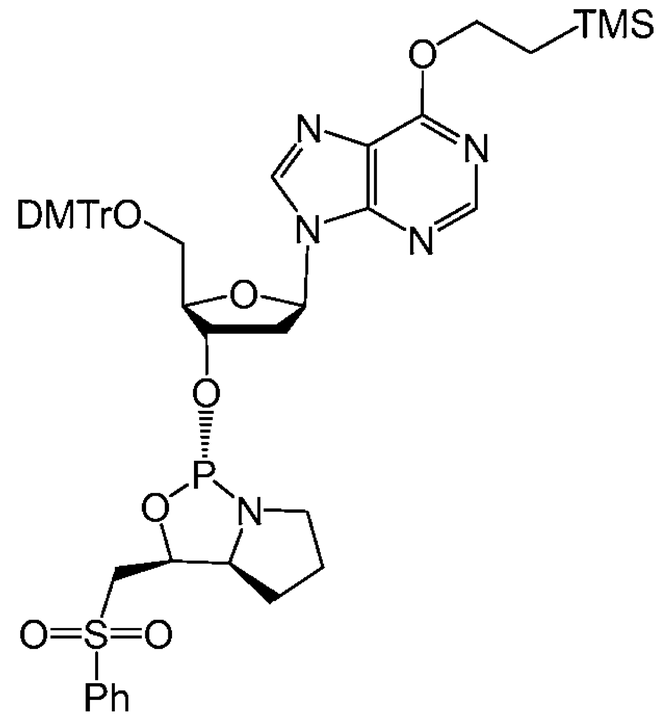


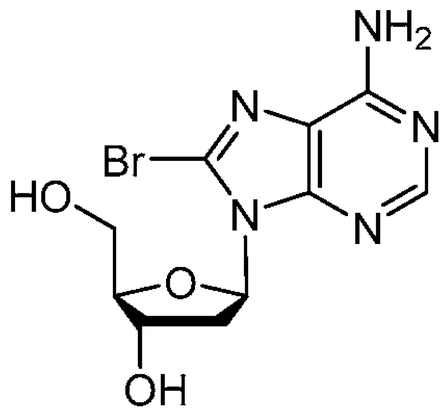


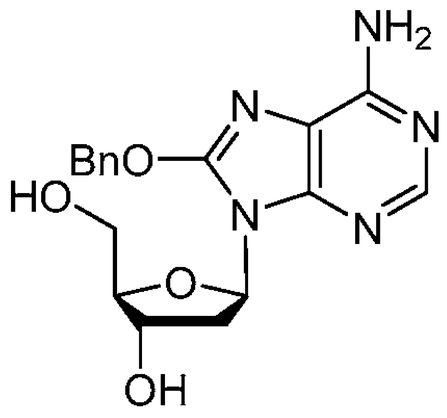


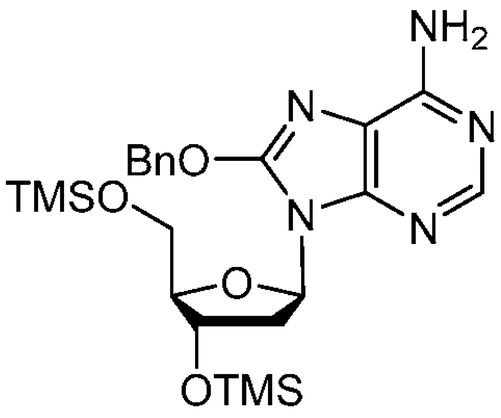


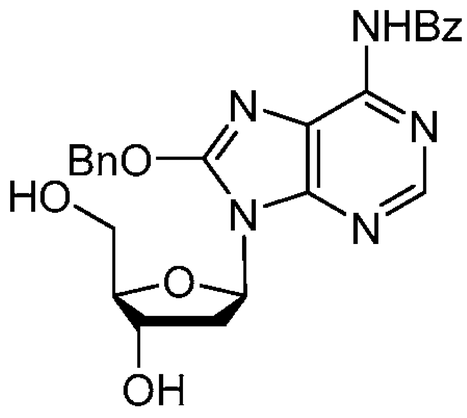


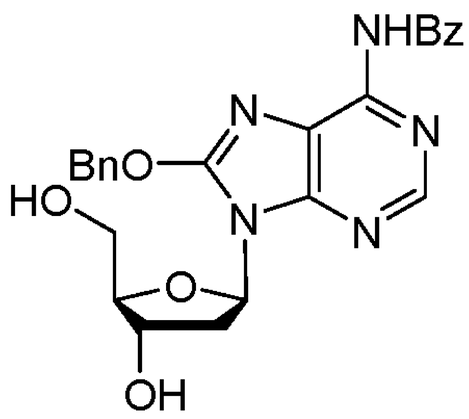


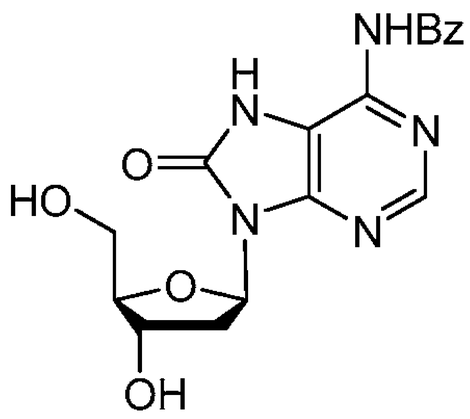


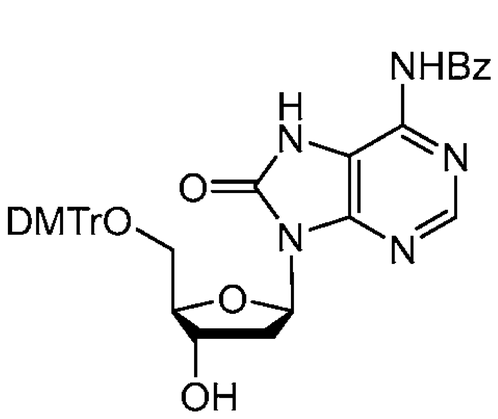


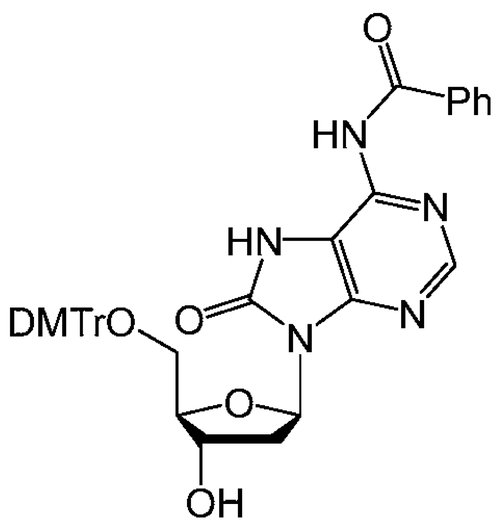


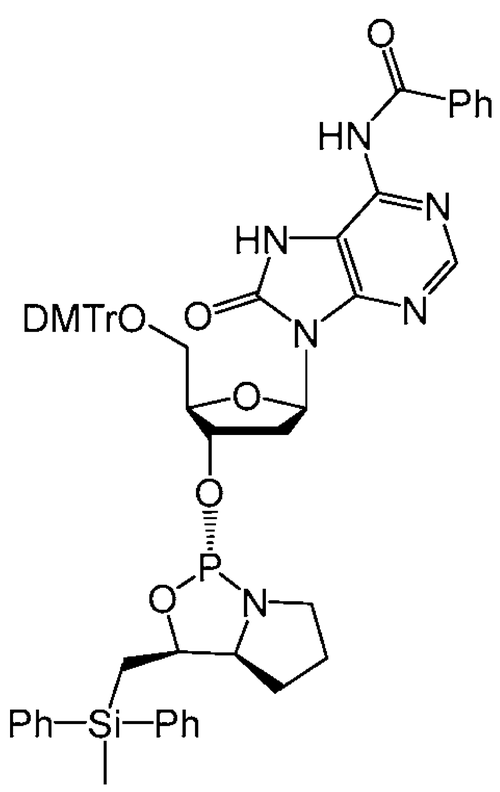


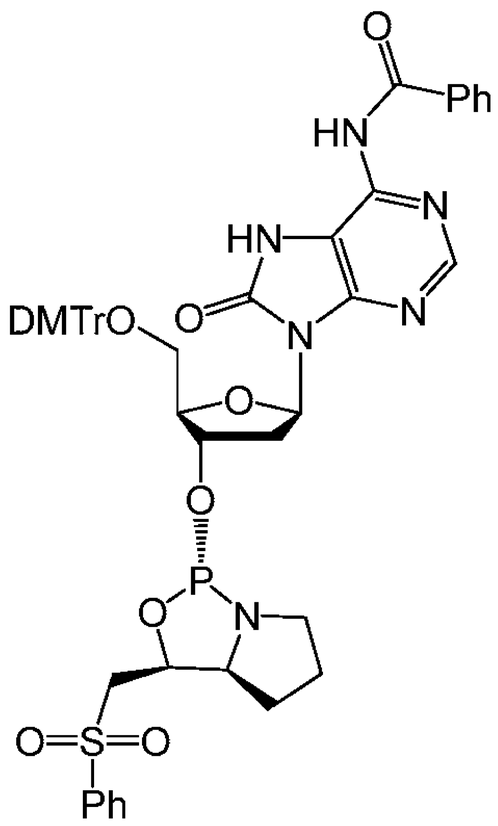


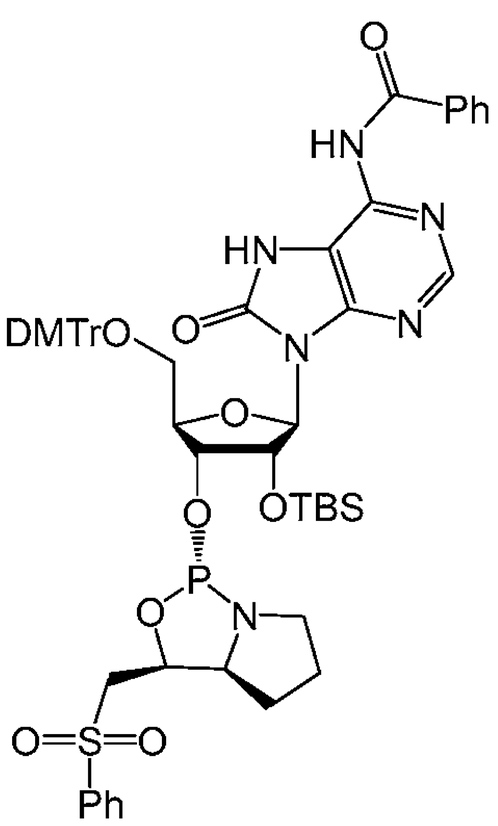


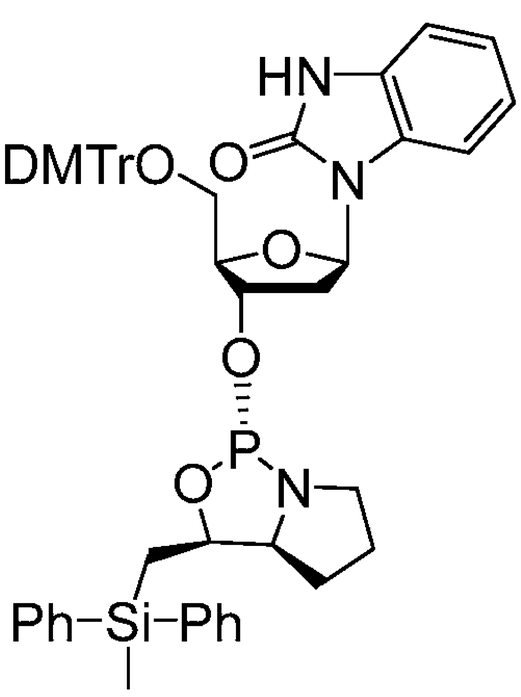


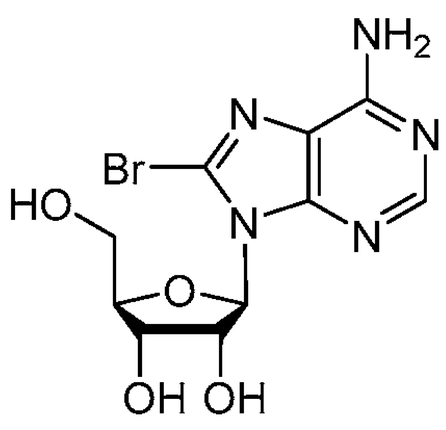


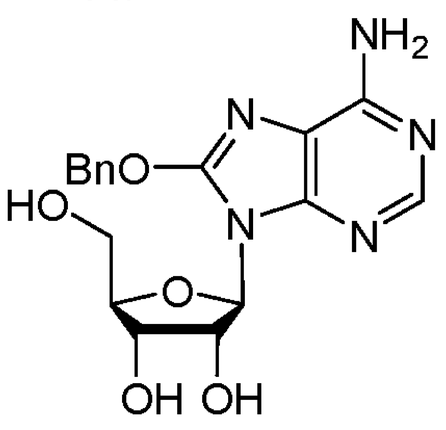


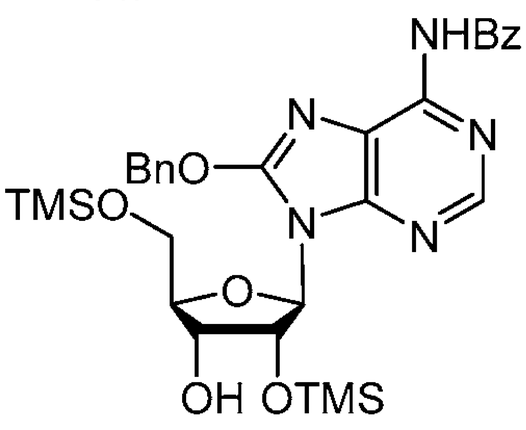


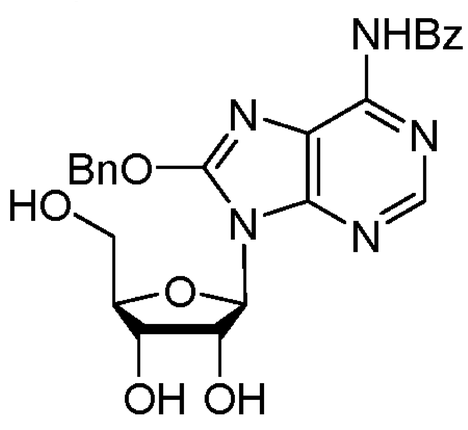


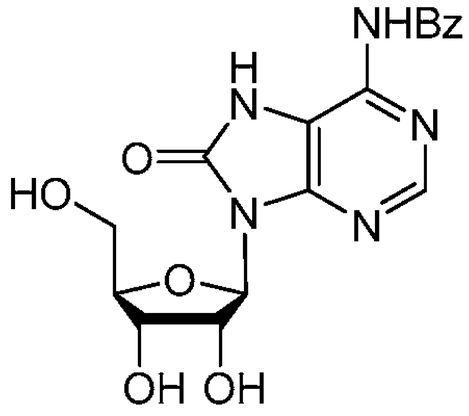


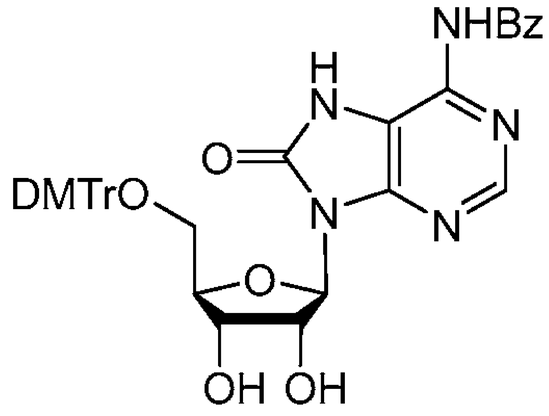


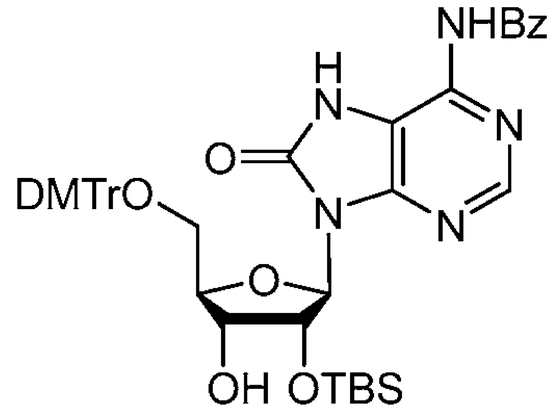


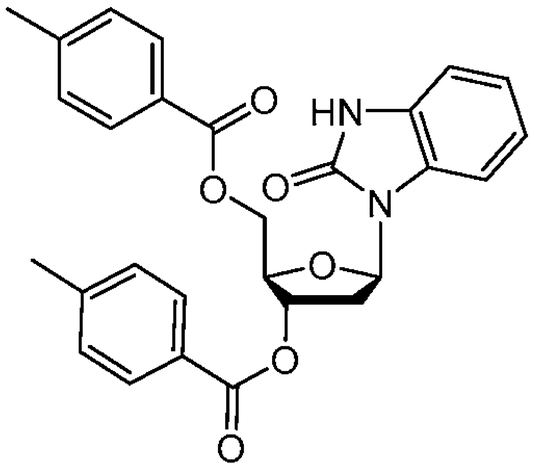


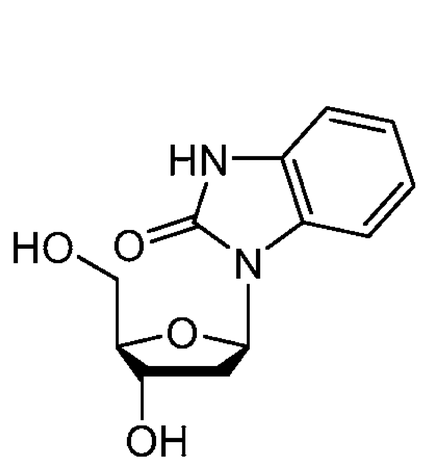


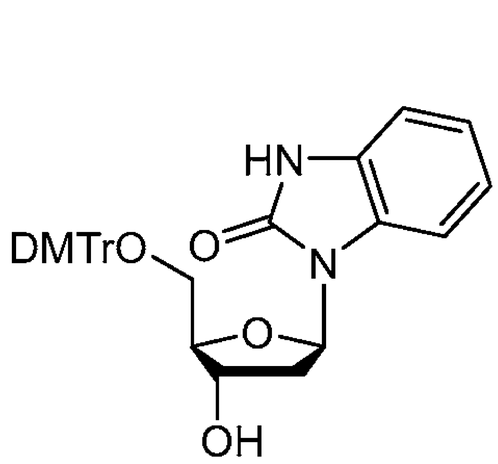


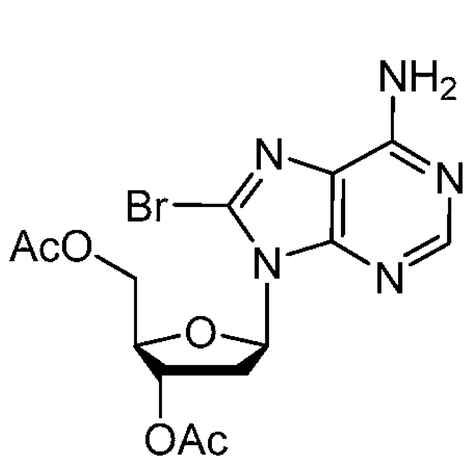


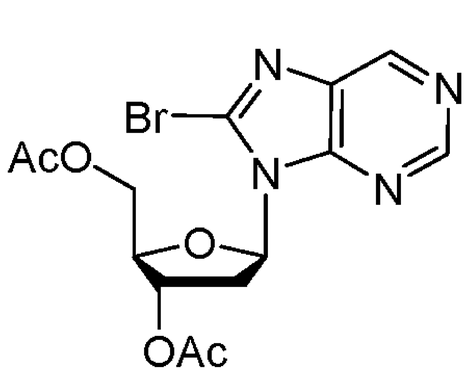


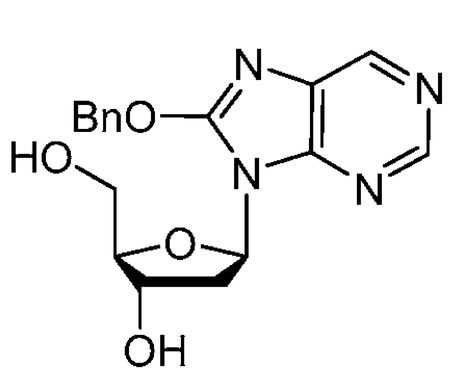


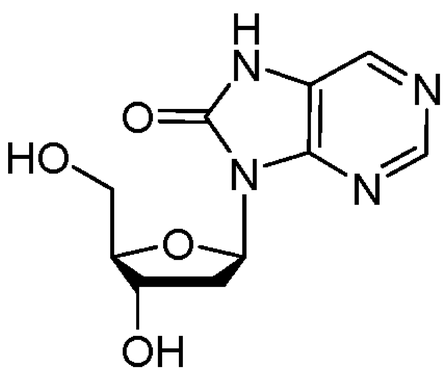


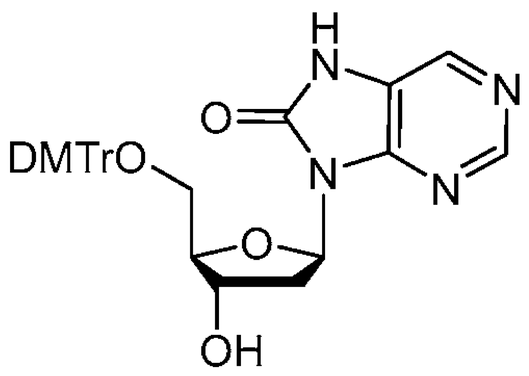


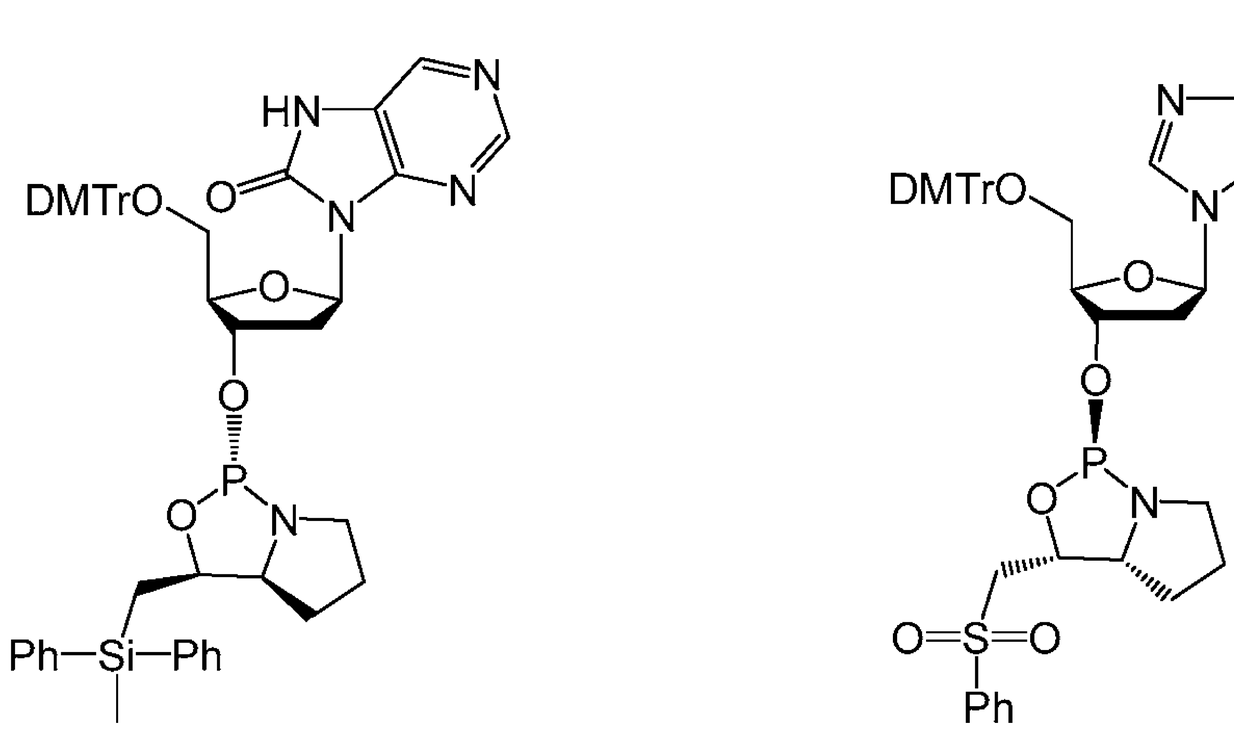


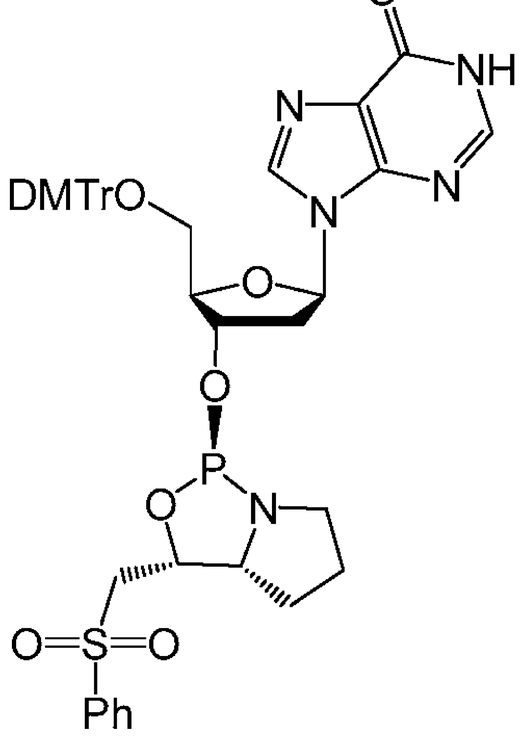


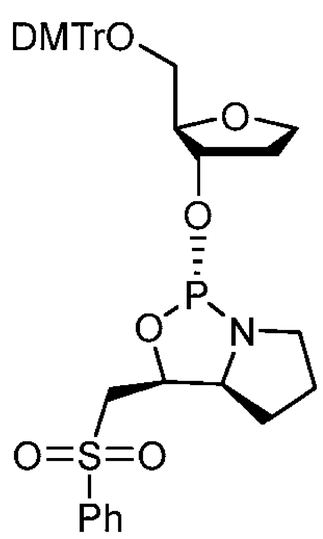


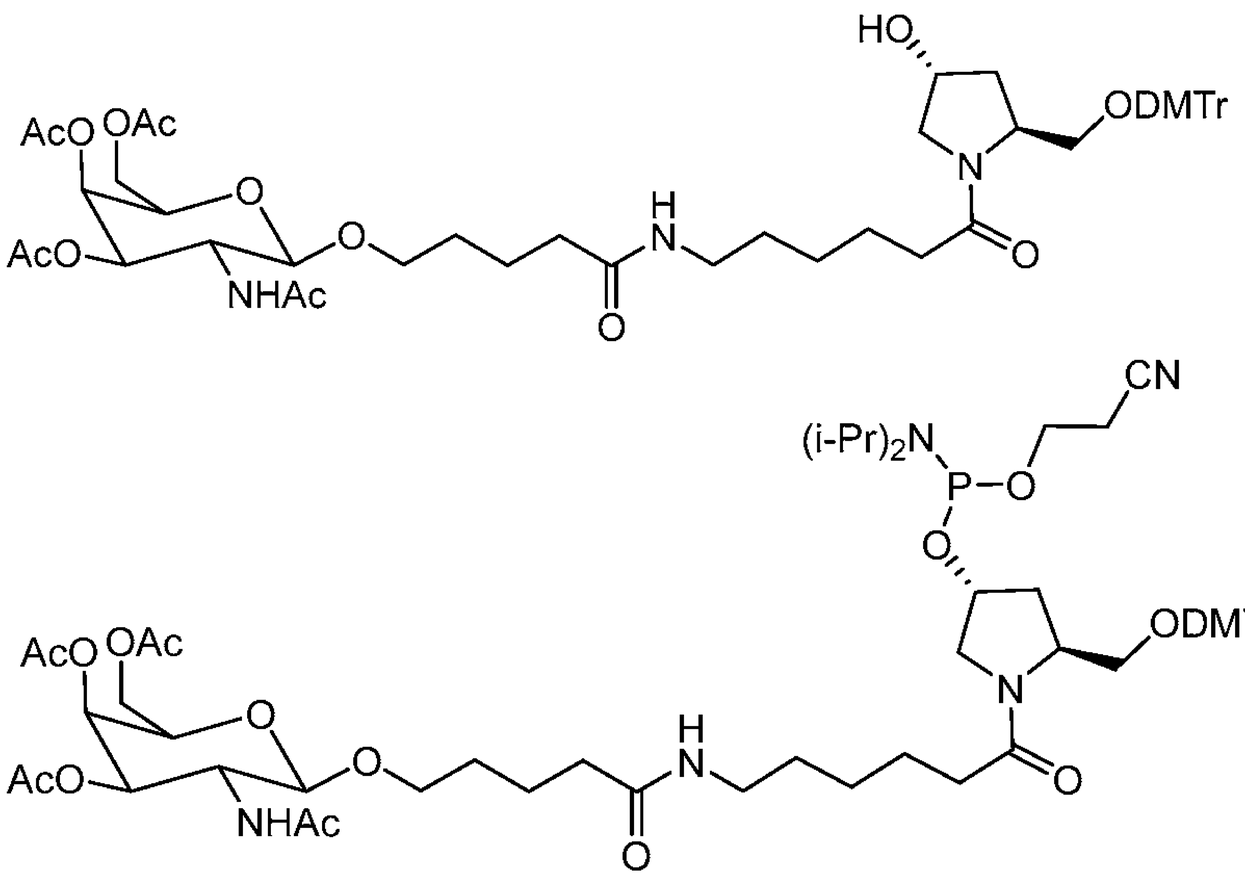






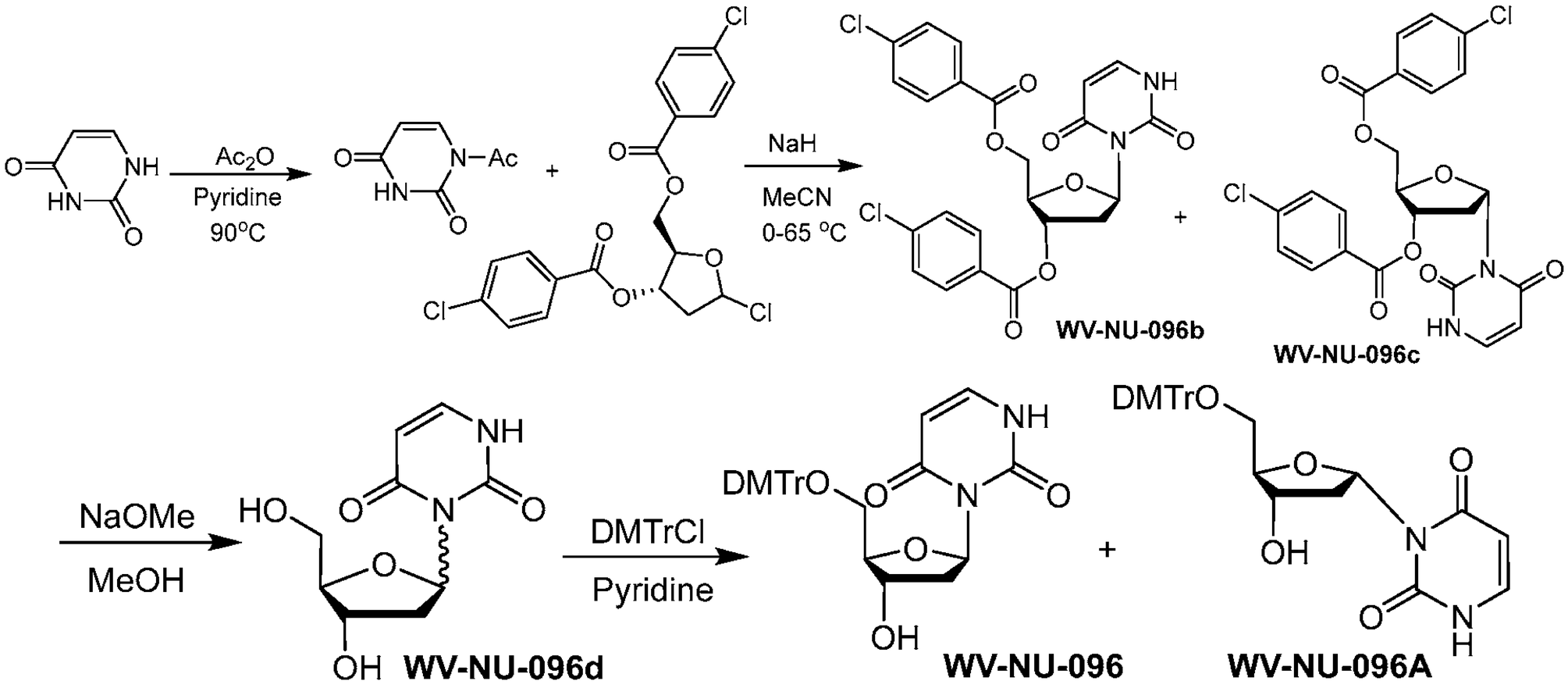


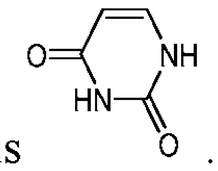
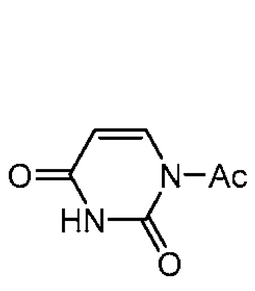
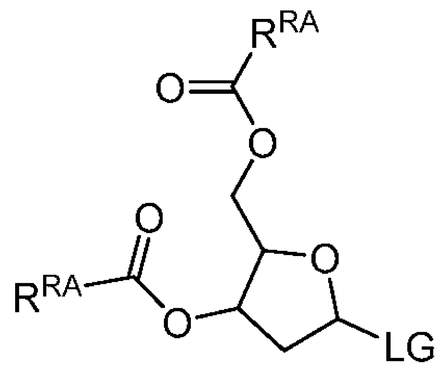


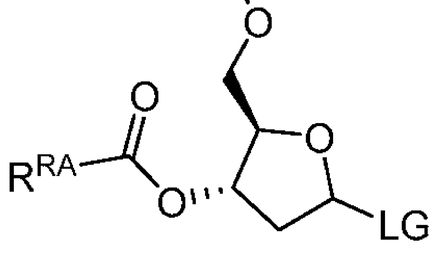
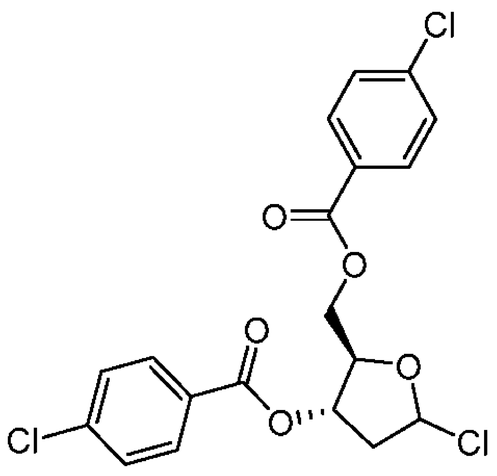
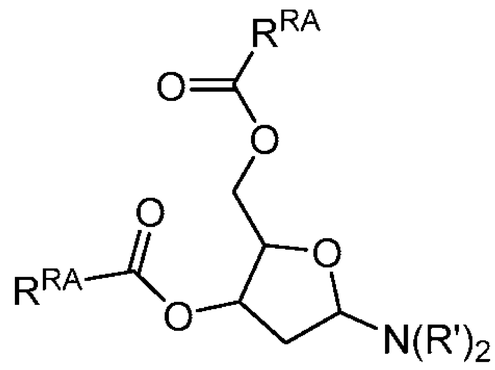
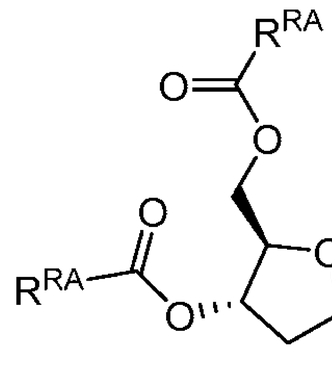
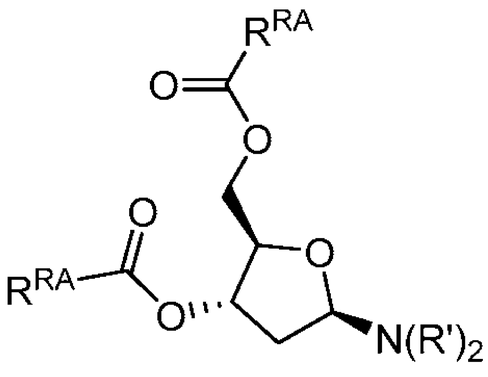
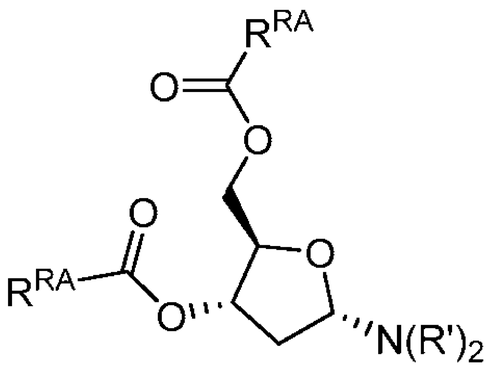
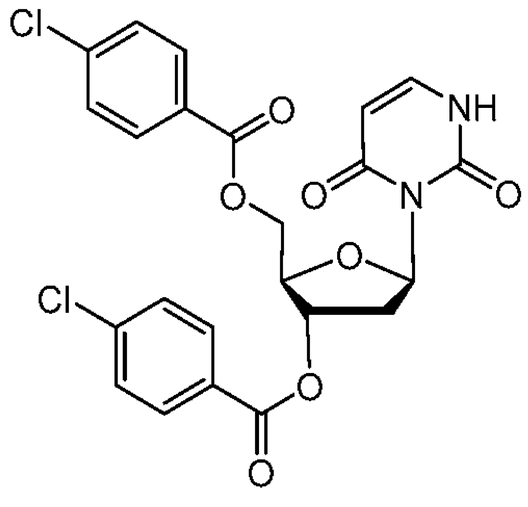


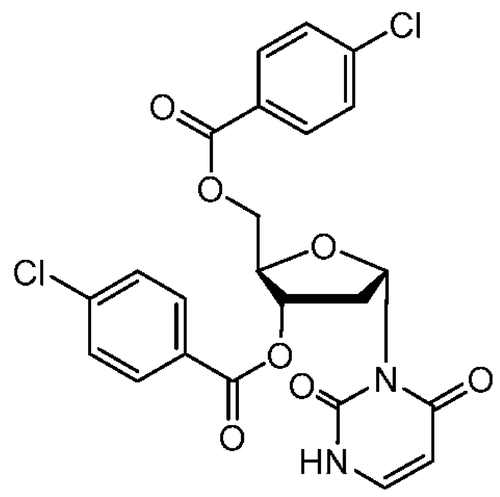
[001147] Certain useful technologies for preparing various additional useful compounds are described below as examples.

[001148] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-096) and 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-096A)

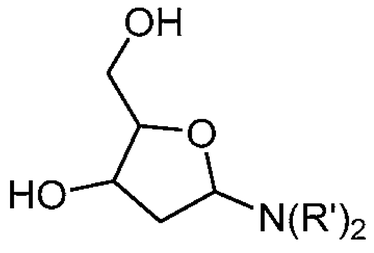


[001149] In some embodiments, the present disclosure provides compounds and methods for preparing nucleobases, sugars, nucleosides, etc. In some embodiments, a compound has the structure of $NH(R')_2$ or a salt thereof, wherein each R' is as described herein. In some embodiments, two R' are taken together with the nitrogen to which they are attached to form an optionally substituted ring. In some embodiments, a formed ring is an optionally substituted monocyclic saturated, partially unsaturated or aromatic ring having 0-2 heteroatoms in addition to the nitrogen. In some embodiments, $NH(R')_2$ is a nucleobase. In some embodiments, a compound is  . In some embodiments, NH(R') or a nucleobase is properly protected so that reactions selectively occurs at a desired amino group. In some embodiments, a compound is  . In some embodiments, a compound has the structure of  , wherein LG is a leaving group, and each R^{RA} is independently substituted C_{6-10} aryl or C_{5-10} heteroaryl having 1-6 heteroatoms, wherein at least one substituent is independently an electron-withdrawing group. In some embodiments, each substituent is independently an electron-withdrawing group. In some embodiments, R^{RA} is substituted aryl wherein a substituent is an electron-withdrawing group. In some embodiments, each R^{RA} is independently

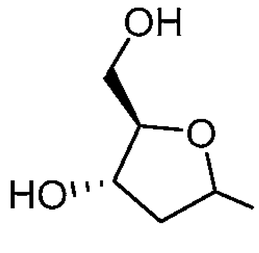
substituted aryl wherein a substituent is an electron-withdrawing group. In some embodiments, an electron-withdrawing group is −Cl. In some embodiments, R^{RA} is p-chlorophenyl. In some embodiments, each R^{RA} is p-chlorophenyl. In some embodiments, a leaving group is −Cl. Those skilled in the art appreciate that various electron-withdrawing groups and leaving groups may be utilized in accordance with the present disclosure. In some embodiments, a compound is  , wherein each variable is independently as described herein. In some embodiments, a compound is  . In some embodiments, a compound is  . In some embodiments, a compound is  . In some embodiments, a compound is  . In some embodiments, a compound is  . In some embodiments, a compound is  . In some



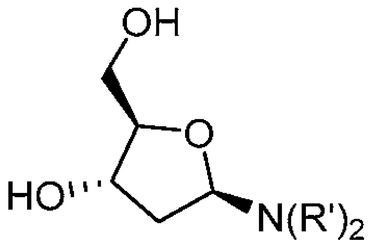
embodiments, a compound is . In some embodiments, a compound is



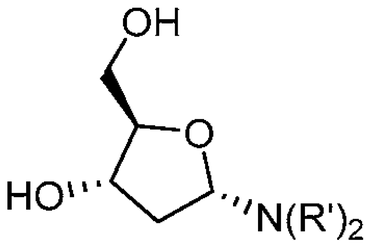
. In some embodiments, a compound is



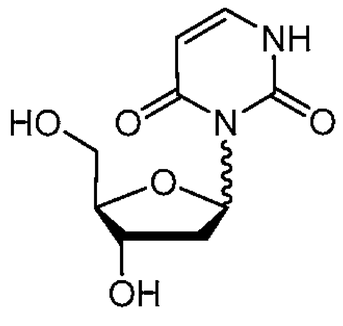
. In some embodiments, a compound is



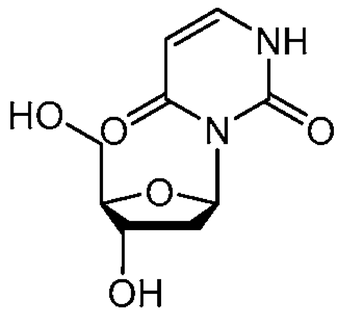
. In some embodiments, a compound is



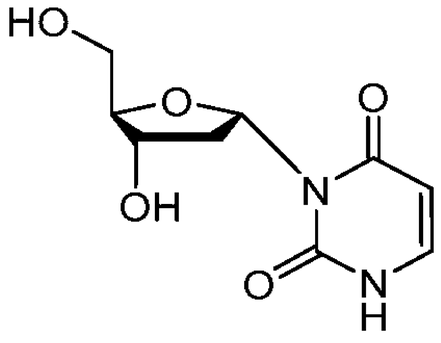
. In some embodiments, a compound is



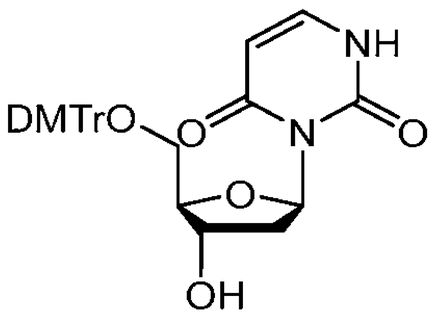
. In some embodiments, a compound is



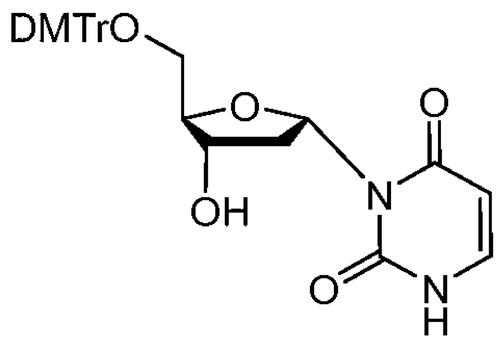
. In some embodiments, a compound is



. In some embodiments, a compound is

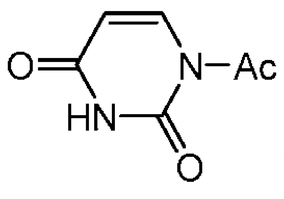


. In some embodiments, a compound is

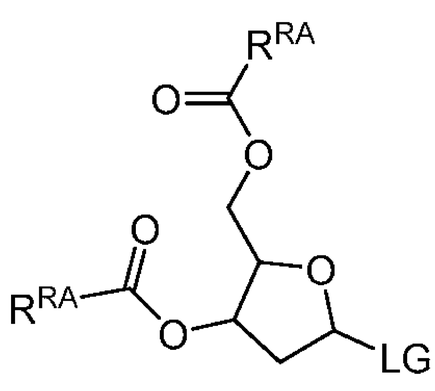


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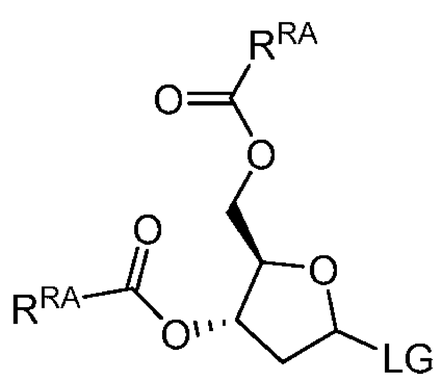
[001150] In some embodiments, the present disclosure provides a method, comprising reacting a compound selected from a compound having the structure of $NH(R')_2$, a nucleobase and an amine, or salt thereof (e.g.,

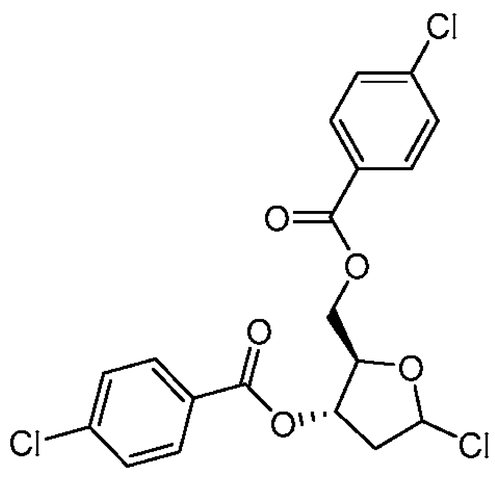


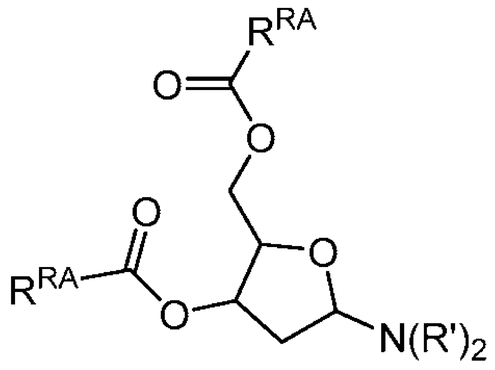
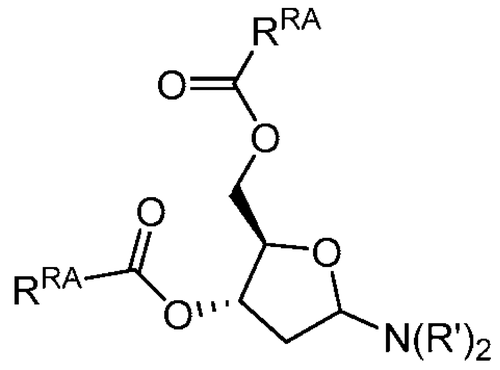
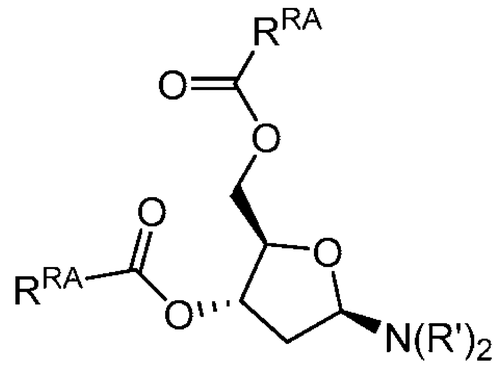
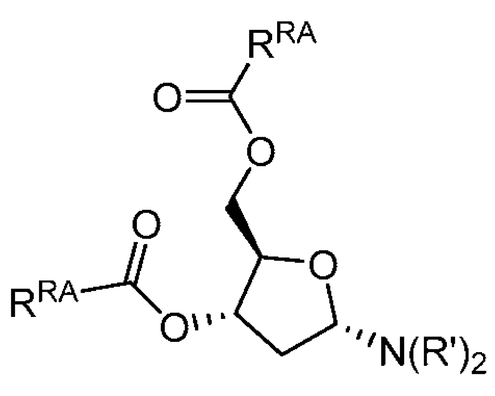
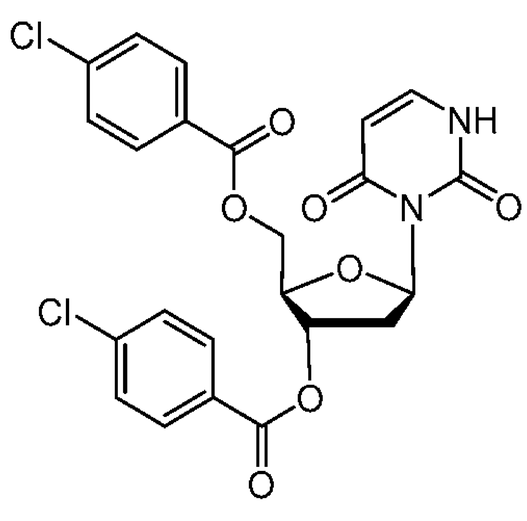
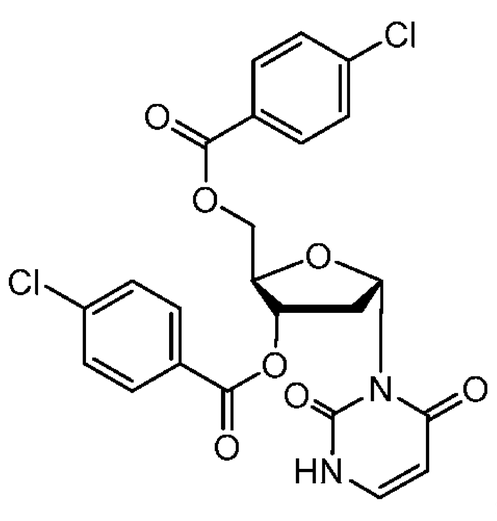
) with a compound having the structure of

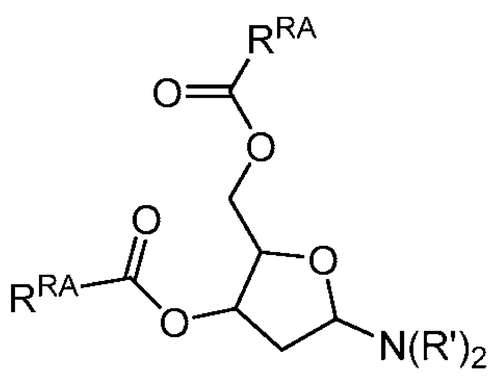
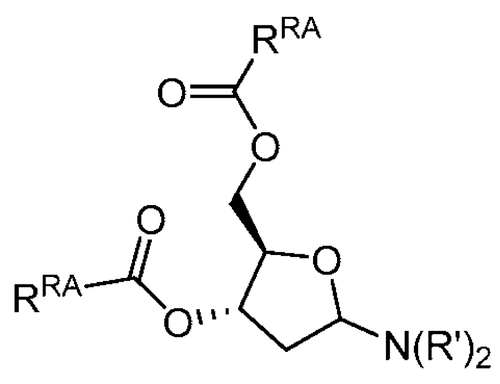
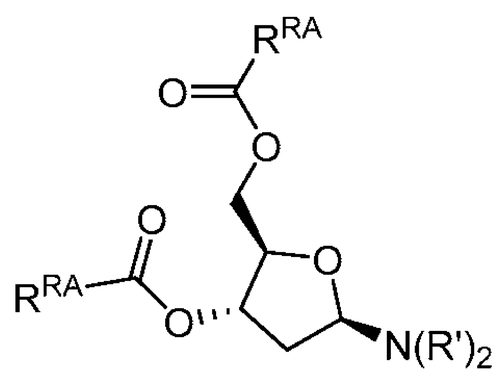
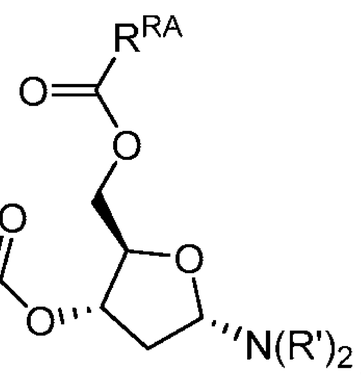
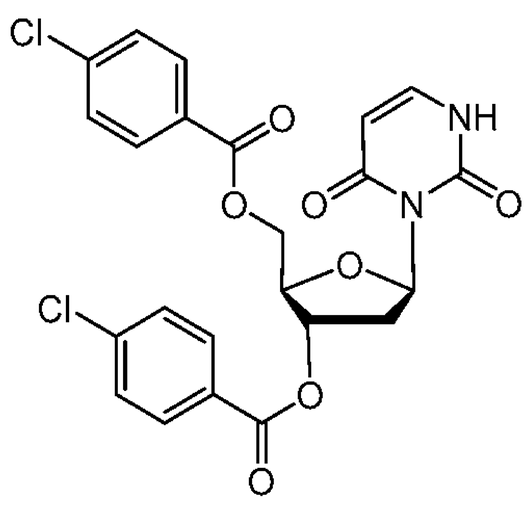
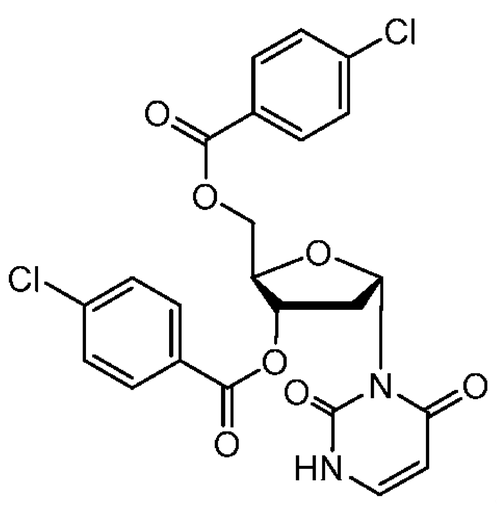
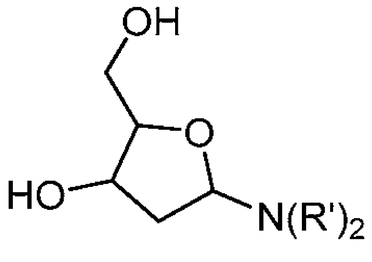
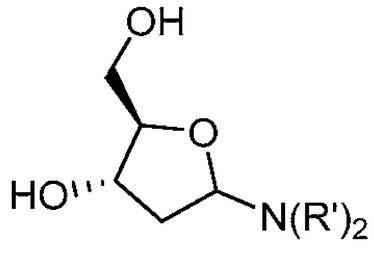
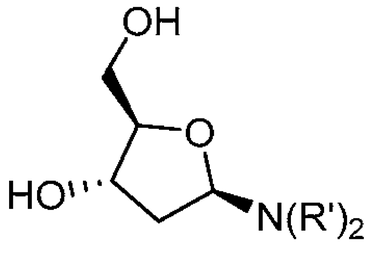


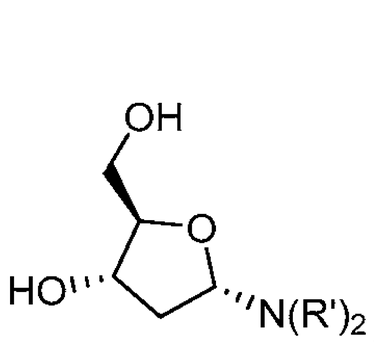
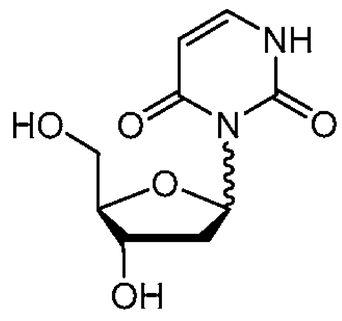
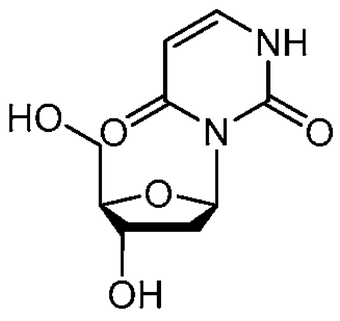
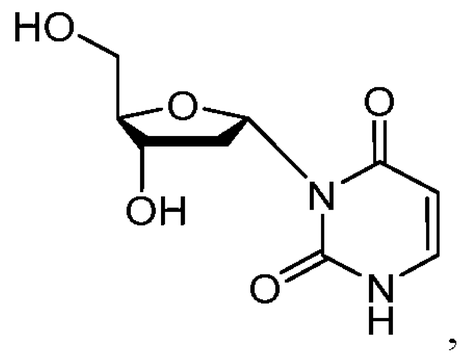
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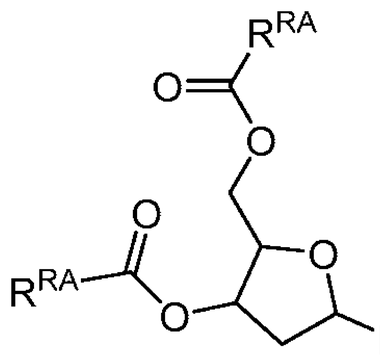

, etc.) or a salt thereof to provide a compound having the structure of


(e.g., 
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, etc.) or a salt thereof. In some embodiments, a reaction is performed under a basic condition, e.g., in the presence of NaH. In some embodiments, a suitable solvent is MeCN. In some embodiments, a suitable temperature is 0 to 65 °C. In some embodiments, a provided method comprises converting a compound having the structure of

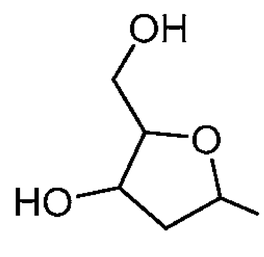

(e.g., 
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, etc.) or a salt thereof into a compound having the structure of 
(e.g., 
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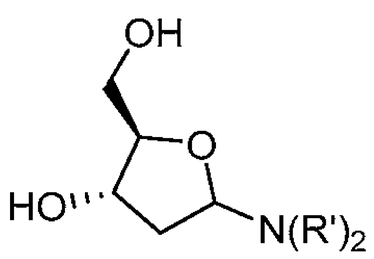
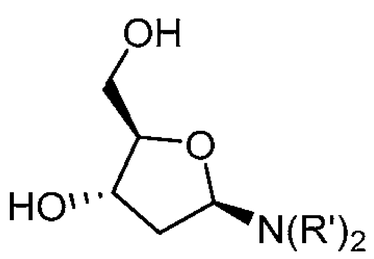
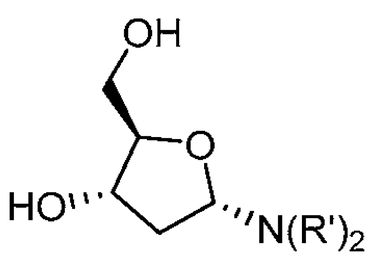
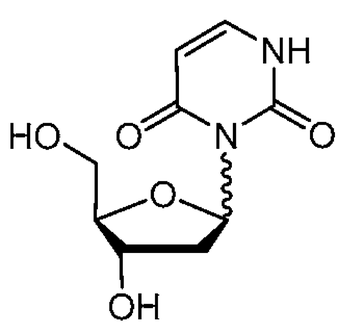
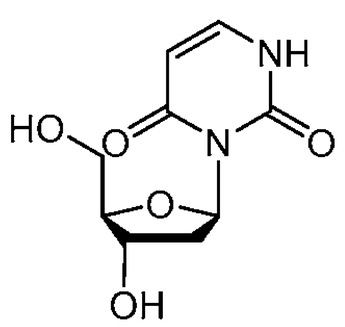
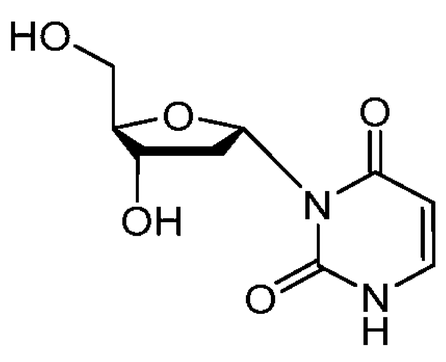
, etc.) or a salt thereof. In some embodiments, a conversion is performed under an ester hydrolysis condition. In some embodiments, a conversion comprises contacting a compound having the structure of



or a salt thereof with a base (e.g., NaOMe) in a suitable solvent (e.g., an alcohol such as MeOH). In some embodiments, a method comprises protecting a 5'-OH of a compound having the structure of



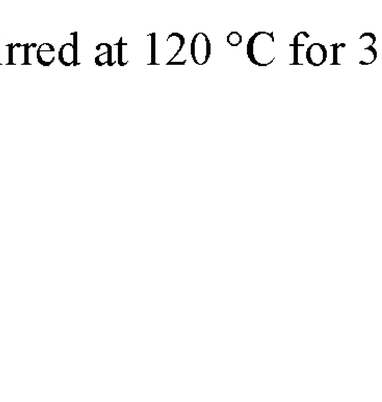
(e.g.,

, etc.) or a salt thereof to provide a compound having the structure of

(e.g.,





,

, etc.) or a salt thereof, wherein PGO is a protected −OH group. In some embodiments, PGO as DMTrO.

[001151] **Step 1.** To a solution of pyrimidine-2,4(1H,3H)-dione (100 g, 892.17 mmol, 1 *eq*) in PYRIDINE (1000 mL) was added Ac_2O (546.48 g, 5.35 mol, 501.36 mL, 6 *eq*). The mixture was stirred at 120 °C for 3

hr. The reaction mixture was concentrated under reduced pressure to give a crude and the residue was washed with EtOAc (100 mL), filtered and the cake was dried under reduced pressure to get the product. 1-Acetylpyrimidine-2,4(1H,3H)-dione (100 g, 648.83 mmol, 72.73% yield) was obtained as a white solid. ^{1}HNMR (400MHz, DMSO-d_6) δ = 11.55 (br s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 5.80 (dd, *J* = 2.2, 8.5 Hz, 1H), 2.70 - 2.55 (m, 3H); TLC (Petroleum ether: Ethyl acetate = 0:1), Rf = 0.72.

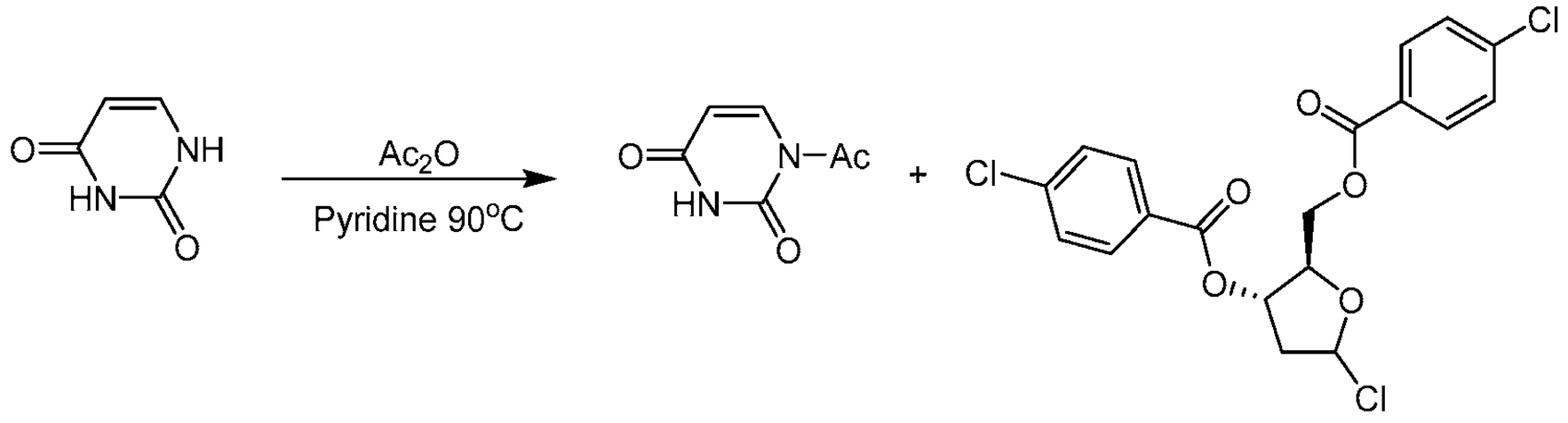
[001152] **Step 2.** A clean and dry three-neck 3 Lit round bottom flask charge with 1-acetylpyrimidine-2,4(1H,3H)-dione (17 g, 110.30 mmol, 1 *eq*) and dissolved into dry MeCN (1700 mL) under argon atmosphere. The reaction mixture was cooled to 0 °C by using ice bath. NaH (6.62 g, 165.45 mmol, 60% purity, 1.5 *eq*) was added portion wise to the reaction mixture and stir for 30 min at 0 °C. (2R,3S)-5-Chloro-2-(((4-chlorobenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-chlorobenzoate (65.88 g, 153.32 mmol, 1.39 *eq*) was added portion wise and stir the reaction mixture for 30 min at 0 °C and 65 °C for 3 h. TLC (Petroleum ether: Ethyl acetate=1:1, Rf=0.24) show that reactant 1 was consumed and new spots was formed. Then, cool the reaction mixture to rt and filter through sintered funnel using Whatman filter paper. The filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (100-200 mesh). The product was eluted with 50% to 80% EtOAc: Petroleum ether, and then the solid was triturated with DCM (30 mL) to give a mixture of compound **WV-NU-096b** and compound **WV-NU-096c** (50 g) as a yellow solid.

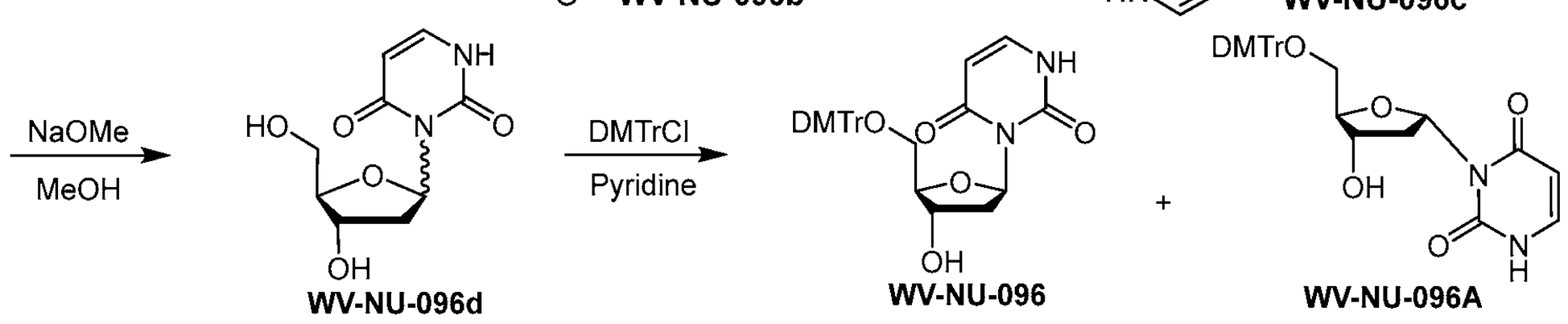
[001153] **Step 3.** To a solution of a mixture of WV-NU-096b and WV-NU-096c (45 g, 89.06 mmol, 1 *eq*) a in MeOH (500 mL) was added NaOMe (12.03 g, 222.65 mmol, 2.5 *eq*). The mixture was stirred at 15 °C for 2 hr. 12.03g NH4Cl was added to the mixture, and it was stirred for 30 min, then filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to 0/1, then ethyl acetate/ methanol=5/1) to give WV-NU-096d (20 g, 87.64 mmol, 98.41% yield) as a yellow solid. LCMS: (M + H^+) = 227.0

[001154] **Step 4.** To a solution of WV-NU-096d (20.00 g, 87.64 mmol, 1 *eq*) in Pyridine (200 mL) was added DMTCl (35.26 g, 104.07 mmol, 1.19 *eq*). The mixture was stirred at 15 °C for 12 hr. The reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate 400 mL (200 mL * 2). The combined organic layers were washed with sat brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (column: Phenomenex Titank C18 Bulk 250*70mm 10u;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 45%-75%,20min) to give **WV-NU-096** (30 g, 55.27 mmol, 63.06% yield, 97.75% purity) and **WV-NU-096A** (5 g, 9.20 mmol, 10.50% yield, 97.61% purity) as white solids. **WV-NU-096:** ^{1}HNMR (400 MHz, DMSO-d_6) δ = 11.14 - 10.94 (m, 1H), 7.47 - 7.31 (m, 3H), 7.27 - 7.21 (m, 6H), 7.20 - 7.13 (m, 1H), 6.86 - 6.77 (m, 4H), 6.61 - 6.52 (m, 1H), 5.57 - 5.49 (m, 1H), 5.08 - 5.02 (m, 1H), 4.29 - 4.19 (m, 1H), 3.87 - 3.76 (m, 1H), 3.74 - 3.69 (m, 6H), 3.24 - 3.16 (m, 1H), 3.08 - 3.01 (m, 1H), 2.62 - 2.52 (m, 1H), 2.04 - 1.92 (m, 1H); LCMS (M-H+):529.2, LCMS purity: 97.75% . **WV-NU-096A:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.25 - 11.01 (m, 1H), 7.49 - 7.43 (m, 1H), 7.41 - 7.35 (m, 2H), 7.33 - 7.28 (m, 2H), 7.27 - 7.17 (m, 5H), 6.95 - 6.84 (m, 4H), 6.57 - 6.44 (m, 1H), 5.63 - 5.56 (m,

1H), 5.28 - 5.19 (m, 1H), 4.34 - 4.24 (m, 1H), 4.12 - 3.99 (m, 1H), 3.77 - 3.69 (m, 6H), 3.17 - 3.10 (m, 1H), 2.98 - 2.89 (m, 1H), 2.60 - 2.53 (m, 1H), 2.38 - 2.30 (m, 1H); LCMS (M-H+):529.2, LCMS purity: 97.61%.

[001155] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-096) and 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-096A)





[001156] Step 1. To a solution of pyrimidine-2,4(1H,3H)-dione (100 g, 892.17 mmol, 1 *eq*) in PYRIDINE (1000 mL) was added Ac_2O (546.48 g, 5.35 mol, 501.36 mL, 6 *eq*). The mixture was stirred at 120 °C for 3 hr. The reaction mixture was concentrated under reduced pressure to give a crude and the residue was washed with EtOAc (100 mL), filtered and the cake was dried under reduced pressure to get the product. 1-Acetylpyrimidine-2,4(1H,3H)-dione (100 g, 648.83 mmol, 72.73% yield) was obtained as a white solid. ^{1}HNMR (400MHz, DMSO-d_6) δ = 11.55 (br s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 5.80 (dd, *J* = 2.2, 8.5 Hz, 1H), 2.70 - 2.55 (m, 3H); TLC (Petroleum ether: Ethyl acetate = 0:1), Rf = 0.72.

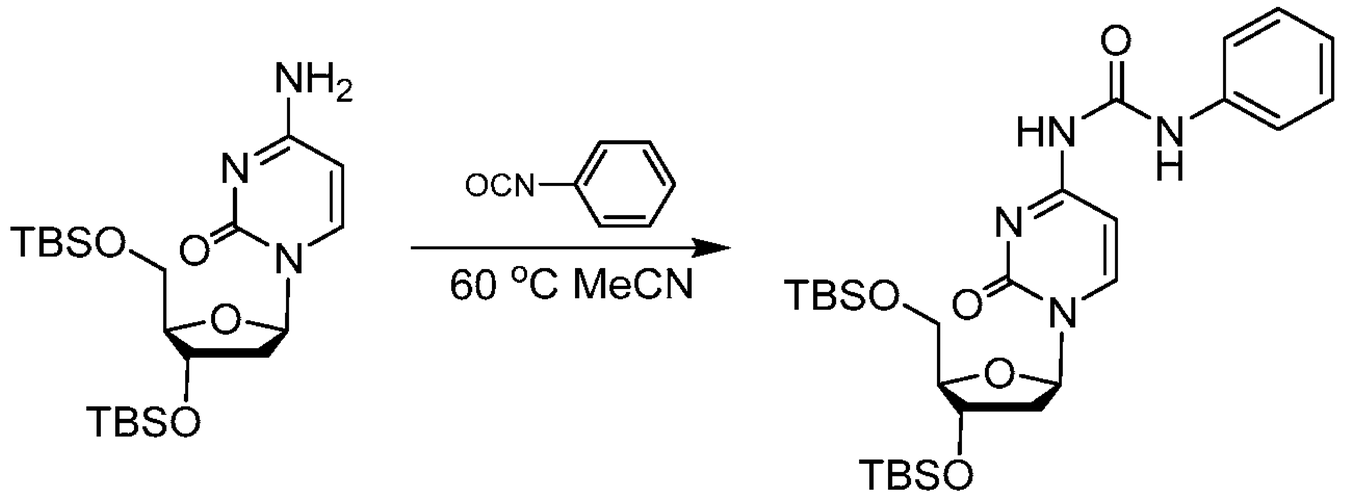
[001157] Step 2. A clean and dry three-neck 3 Lit round bottom flask charge with 1-acetylpyrimidine-2,4(1H,3H)-dione (17 g, 110.30 mmol, 1 *eq*) and dissolved into dry MeCN (1700 mL) under argon atmosphere. The reaction mixture was cooled to 0 °C by using ice bath. NaH (6.62 g, 165.45 mmol, 60% purity, 1.5 *eq*) was added portion wise to the reaction mixture and stir for 30 min at 0 °C. (2R,3S)-5-Chloro-2-(((4-chlorobenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-chlorobenzoate (65.88 g, 153.32 mmol, 1.39 *eq*) was added

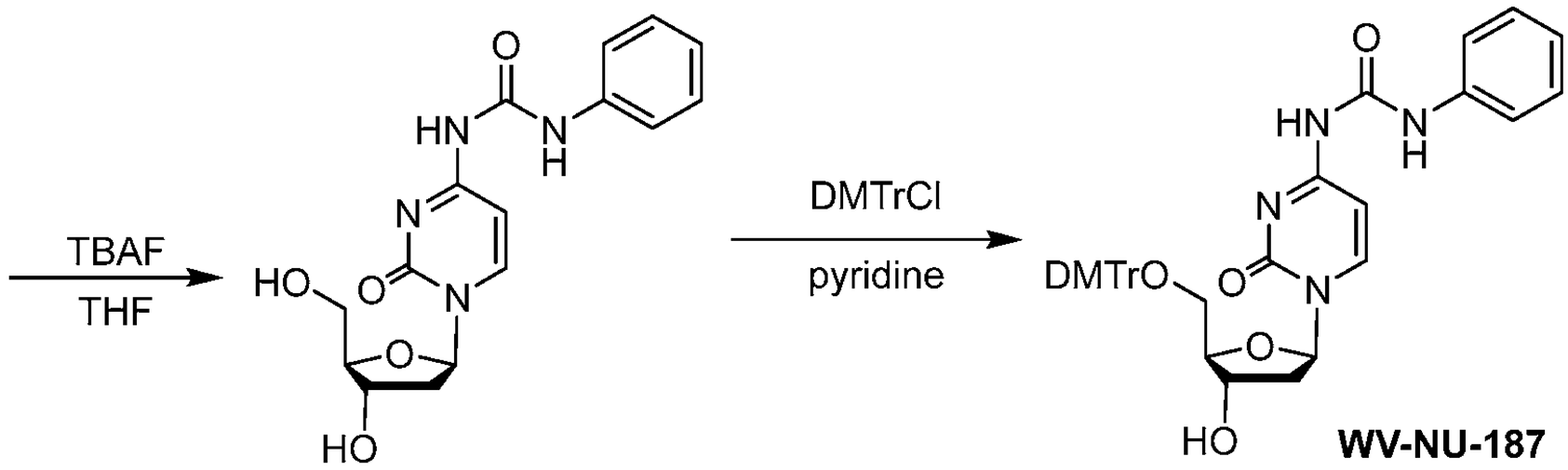
portion wise and stir the reaction mixture for 30 min at 0 °C and 65 °C for 3 h. TLC (Petroleum ether: Ethyl acetate=1:1, Rf=0.24) show that reactant 1 was consumed and new spots was formed. Then, cool the reaction mixture to rt and filter through sintered funnel using Whatman filter paper. The filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (100-200 mesh). The product was eluted with 50% to 80% EtOAc: Petroleum ether, and then the solid was triturated with DCM (30 mL) to give a mixture of compound **WV-NU-096b** and compound **WV-NU-096c** (50 g) as a yellow solid.

[001158] **Step 3.** To a solution of a mixture of WV-NU-096b and WV-NU-096c (45 g, 89.06 mmol, 1 *eq*) a in MeOH (500 mL) was added NaOMe (12.03 g, 222.65 mmol, 2.5 *eq*). The mixture was stirred at 15 °C for 2 hr. 12.03g NH4Cl was added to the mixture, and it was stirred for 30 min, then filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to 0/1, then ethyl acetate/ methanol=5/1) to give WV-NU-096d (20 g, 87.64 mmol, 98.41% yield) as a yellow solid. LCMS: $(M + H^+) = 227.0$

[001159] **Step 4.** To a solution of WV-NU-096d (20.00 g, 87.64 mmol, 1 *eq*) in Pyridine (200 mL) was added DMTCl (35.26 g, 104.07 mmol, 1.19 *eq*). The mixture was stirred at 15 °C for 12 hr. The reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate 400 mL (200 mL * 2). The combined organic layers were washed with sat brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (column: Phenomenex Titank C18 Bulk 250*70mm 10u;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 45%-75%,20min) to give **WV-NU-096** (30 g, 55.27 mmol, 63.06% yield, 97.75% purity) and **WV-NU-096A** (5 g, 9.20 mmol, 10.50% yield, 97.61% purity) as white solids. **WV-NU-096:** ^{1}HNMR (400 MHz, DMSO-d_6) δ = 11.14 - 10.94 (m, 1H), 7.47 - 7.31 (m, 3H), 7.27 - 7.21 (m, 6H), 7.20 - 7.13 (m, 1H), 6.86 - 6.77 (m, 4H), 6.61 - 6.52 (m, 1H), 5.57 - 5.49 (m, 1H), 5.08 - 5.02 (m, 1H), 4.29 - 4.19 (m, 1H), 3.87 - 3.76 (m, 1H), 3.74 - 3.69 (m, 6H), 3.24 - 3.16 (m, 1H), 3.08 - 3.01 (m, 1H), 2.62 - 2.52 (m, 1H), 2.04 - 1.92 (m, 1H); LCMS (M-H+):529.2, LCMS purity: 97.75% . **WV-NU-096A:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.25 - 11.01 (m, 1H), 7.49 - 7.43 (m, 1H), 7.41 - 7.35 (m, 2H), 7.33 - 7.28 (m, 2H), 7.27 - 7.17 (m, 5H), 6.95 - 6.84 (m, 4H), 6.57 - 6.44 (m, 1H), 5.63 - 5.56 (m, 1H), 5.28 - 5.19 (m, 1H), 4.34 - 4.24 (m, 1H), 4.12 - 3.99 (m, 1H), 3.77 - 3.69 (m, 6H), 3.17 - 3.10 (m, 1H), 2.98 - 2.89 (m, 1H), 2.60 - 2.53 (m, 1H), 2.38 - 2.30 (m, 1H); LCMS (M-H+):529.2, LCMS purity: 97.61%.

[001160] Synthesis of 1-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea (WV-NU-187)





WV-NU-187

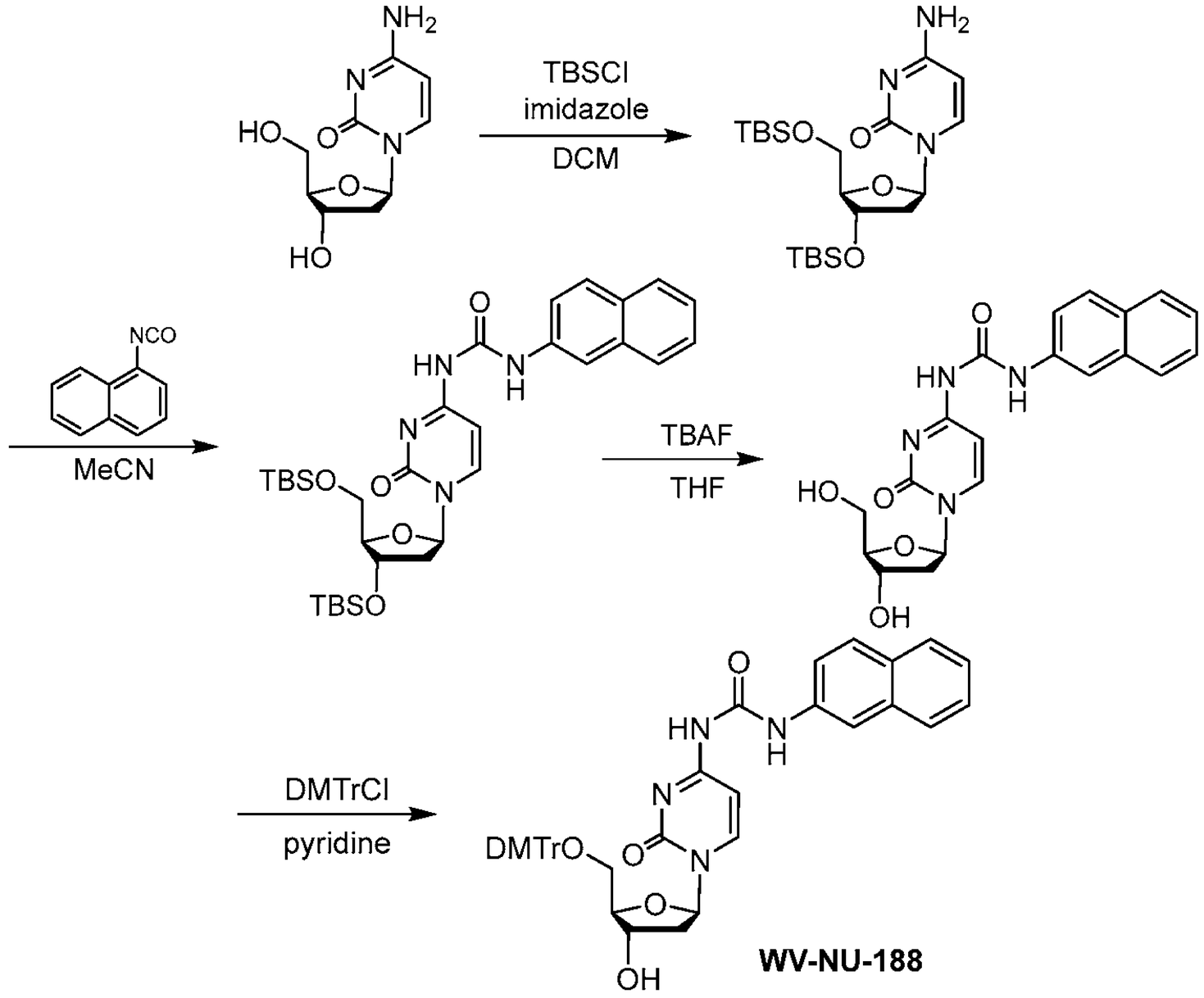
[001161] Step 1. To a solution of 4-amino-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (98 g, 215.04 mmol, 1 *eq.*) in ACN (1000 mL) was added isocyanatobenzene (29.93 g, 251.26 mmol, 27.21 mL, 1.17 *eq.*). The mixture was stirred at 20°C for 6 hr. The reaction mixture was filtered, the solid was desired. The filtrate was quenched by addition water 100 mL. The solid was washed with ACN (300 mL*3). 1-(1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea (90 g, crude) was obtained as a white solid. LCMS ($M-H^+$): 573.2

[001162] Step 2. To a solution of 1-(1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea (90 g, 156.56 mmol, 1 *eq.*) in THF (900 mL) was added TBAF (1 M, 391.40 mL, 2.5 *eq.*). The mixture was stirred at 20 °C for 3 hr. TLC (Petroleum ether: Ethyl acetate = 0:1, Rf = 0.1) indicated starting material was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Methanol=1/0 to 3/1) to give 1-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea (54 g, crude) as a white solid.

Step 3. To a solution of 1-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea (53 g, 153.03 mmol, 1 *eq.*) in PYRIDINE (500 mL) was added DMTCl (77.78 g, 229.55 mmol, 1.5 *eq.*). The mixture was stirred at 20 °C for 5 hr. The reaction mixture was quenched by addition methanol 200 mL, and then concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give WV-NU-187 (26 g, 39.79 mmol, 76.56% yield, 99.28% purity) as a yellow solid. ^{1}HNMR (400 MHz, CHLOROFORM-d) δ = 11.57 - 10.79 (m, 2H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.68 (br d, *J* = 7.8 Hz, 2H), 7.41 (br d, *J* = 7.6 Hz, 2H), 7.36 - 7.22 (m, 9H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.04 (br t, *J* = 7.3 Hz, 1H), 6.92 - 6.79 (m, 4H), 6.30 (br t, *J* = 5.4 Hz, 1H), 4.45 (br d, *J* = 5.0

Hz, 1H), 4.10 - 4.05 (m, 1H), 3.80 (s, 6H), 3.59 - 3.35 (m, 2H), 2.68 - 2.55 (m, 1H), 2.34 - 2.19 (m, 2H); LCMS ($M-H^+$): 647.3; purity: 99.28%.

[001163] Synthesis of 1-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea (WV-NU-188)



WV-NU-188

[001164] Step 1. Two batches: To a solution of 4-amino-1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (25 g, 110.03 mmol, 1 *eq.*) in DCM (250 mL) was added imidazole (59.92 g, 880.22 mmol, 8 *eq.*) and TBSCl (66.33 g, 440.11 mmol, 53.93 mL, 4 *eq.*). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was diluted with water 500 mL and extracted with dichloromethane (500 mL * 2). The combined organic layers were dried over Na_2SO_4 filtered and concentrated under reduced pressure to give a residue to give 4-amino-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (100 g, crude) as a colorless oil. LCMS ($M-H^+$):454.5, purity: 99.93%

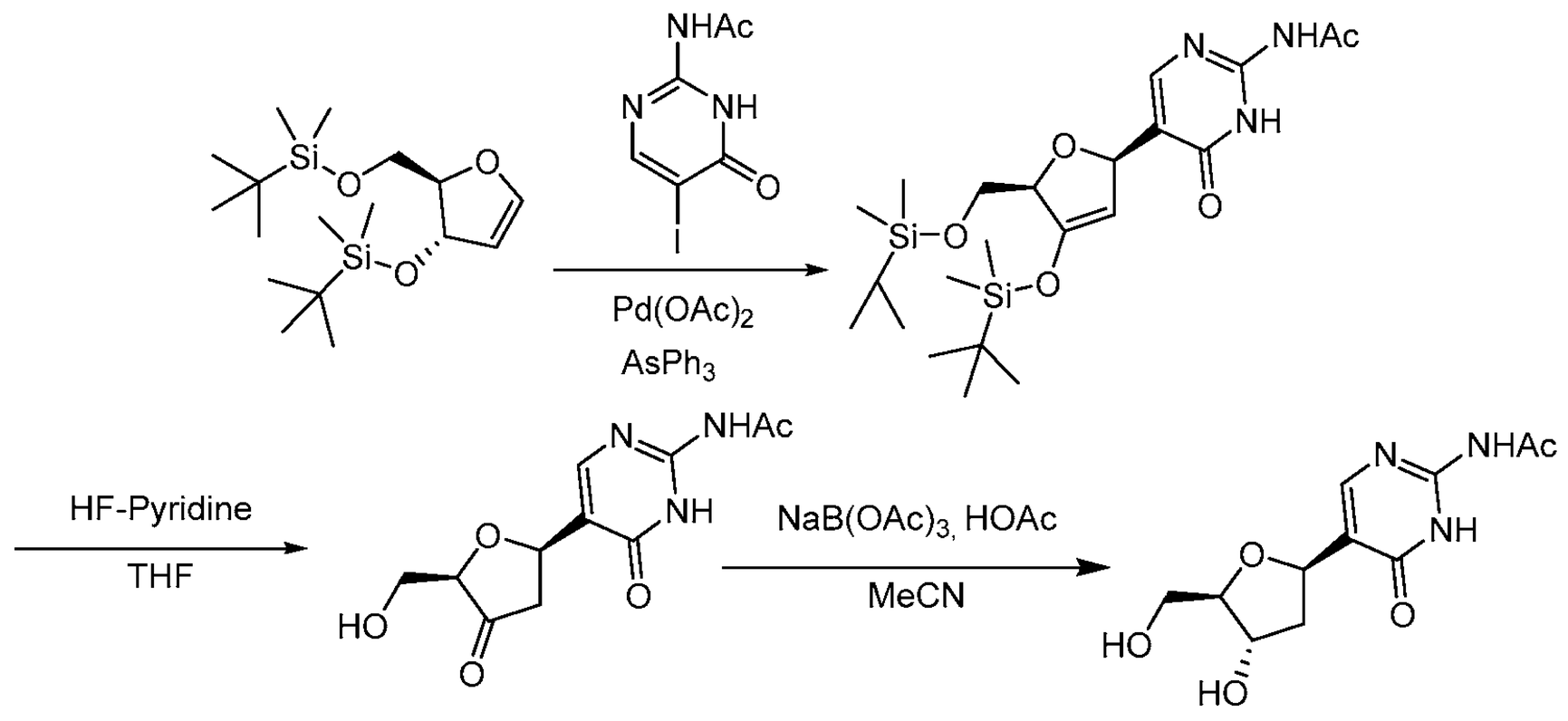
[001165] Step 2. For two batches: To a solution of 4-amino-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (46.5 g, 102.03 mmol, 1 *eq.*) in MeCN (500 mL) was added 1-isocyanatonaphthalene (17.26 g, 102.03 mmol, 14.63 mL, 1 *eq.*). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was diluted with water 500 mL and extracted with DCM (200 mL *2). The combined organic layers were dried over Na_2SO_4 filtered and concentrated under reduced pressure to give 1-(1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea (127 g) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 12.51 (br s, 1H), 10.48 (s, 1H), 8.46 - 7.90

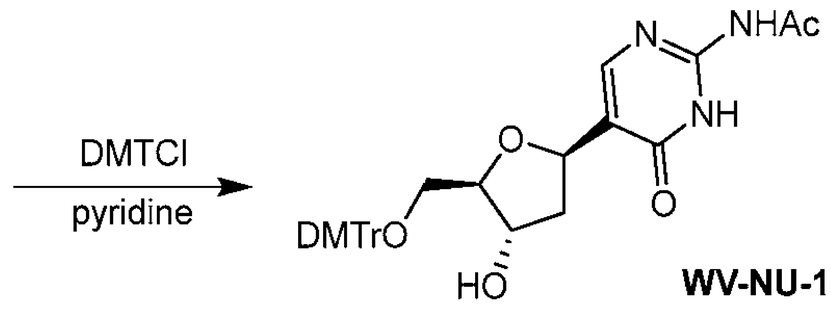
(m, 4H), 7.71 - 7.45 (m, 4H), 6.36 - 6.13 (m, 2H), 4.39 (br d, J = 4.5 Hz, 1H), 3.92 - 3.69 (m, 3H), 2.39 - 2.17 (m, 2H), 0.88 (br d, J = 7.5 Hz, 18H), 0.08 (br d, J = 1.1 Hz, 12H); LCMS ($M-H^+$):622.9, purity: 85.7%

[001166] **Step 3**. For two batches: To a solution of 1-(1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea (63.5 g, 101.61 mmol, 1 *eq.*) in THF (600 mL) was added TBAF (1 M, 254.03 mL, 2.5 *eq.*). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction was added with 500ml ethyl acetate and stirred at 25°C for 30 min to precipitate out solid, which was then filtered to give 1-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea (80 g) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 8.65 - 8.56 (m, 1H), 8.38 (d, J = 7.6 Hz, 1H), 8.08 (br d, J = 7.3 Hz, 1H), 7.89 (br dd, J = 2.9, 6.5 Hz, 1H), 7.58 - 7.39 (m, 4H), 6.36 - 6.18 (m, 2H), 4.33 - 4.25 (m, 1H), 3.81 (br d, J = 3.5 Hz, 1H), 3.69 - 3.57 (m, 2H), 2.27 - 2.18 (m, 1H), 2.05 (td, J = 6.3, 13.0 Hz, 1H); LCMS ($M-H^+$):395.1, purity: 97.74%.

[001167] **Step 4**. For two batches: To a solution of 1-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea (40 g, 100.91 mmol, 1 *eq.*) in pyridine (400 mL) was added DMTCl (51.29 g, 151.36 mmol, 1.5 *eq.*). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with water 800 mL and extracted with Ethyl acetate (400 mL * 4). The combined organic layers were washed with brine 400 mL, dried over Na_2SO_4 filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether: Ethyl acetate = 10:1 to 0:1, 5%TEA) to give **WV-NU-188** (82 g, 117.35 mmol, 58.57% yield) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 10.53 (s, 1H), 8.44 (br d, J = 8.0 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 7.4 Hz, 1H), 7.98 - 7.94 (m, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.64 - 7.55 (m, 2H), 7.50 (t, J = 7.9 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.37 - 7.22 (m, 7H), 6.91 (dd, J = 1.0, 8.9 Hz, 4H), 6.25 - 6.13 (m, 2H), 5.40 (d, J = 4.6 Hz, 1H), 4.34 (quin, J = 5.3 Hz, 1H), 3.74 (s, 6H), 3.30 (br d, J = 3.6 Hz, 2H), 2.44 - 2.35 (m, 1H), 2.28 - 2.19 (m, 1H); LCMS ($M-H^+$): 697.3; purity: 99.66%.

[001168] Synthesis of N-(5-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (WV-NU-189)





WV-NU-189

[001169] **Step 1**. To a solution of BSA (73.19 g, 359.80 mmol, 88.94 mL, 3.1 eq.) was added dropwise to a suspension of N-(5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (80.97 g, 290.16 mmol, 2.5 eq.) in DMF (500 mL) under an argon atmosphere. After stirring for 1 h, the reaction become a clear solution. Then DIPEA (46.50 g, 359.80 mmol, 62.67 mL, 3.1 eq.) and tert-butyl(((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)dimethylsilane (40 g, 116.06 mmol, 1 eq.) were added. In a separate flask, $Pd(OAc)_2$ (1.82 g, 8.12 mmol, 0.07 eq.) was added to a solution of triphenylarsane (14.22 g, 46.43 mmol, 0.4 eq.) in stirring DMF (500 mL). After 30 min, this solution was added slowly to the first flask and the mixture was stirred for 12 hr at 80 °C. The reaction was quenched with the addition of H_2O (30 mL) and the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (500 mL) and washed with H_2O (2*100mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to give N-(5-((2R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (25 g, 50.43 mmol, 43.45% yield) as a white solid. ^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.27 (d, J = 2.0 Hz, 1H), 8.22 (br d, J = 8.0 Hz, 2H), 7.98 (dd, J = 8.6, 2.3 Hz, 1H), 7.30-7.39 (m, 4H), 5.69 (dd, J = 3.8, 1.4 Hz, 1H), 4.75 (s, 1H), 4.58 (tt, J = 3.7, 1.9 Hz, 1H), 3.85-3.92 (m, 1H), 3.75-3.81 (m, 1H), 2.22-2.24 (m, 4H), 0.86-0.98 (m, 19H), 0.22 (d, J = 6.6 Hz, 6H), 0.05 ppm (d, J = 2.5 Hz, 6H).

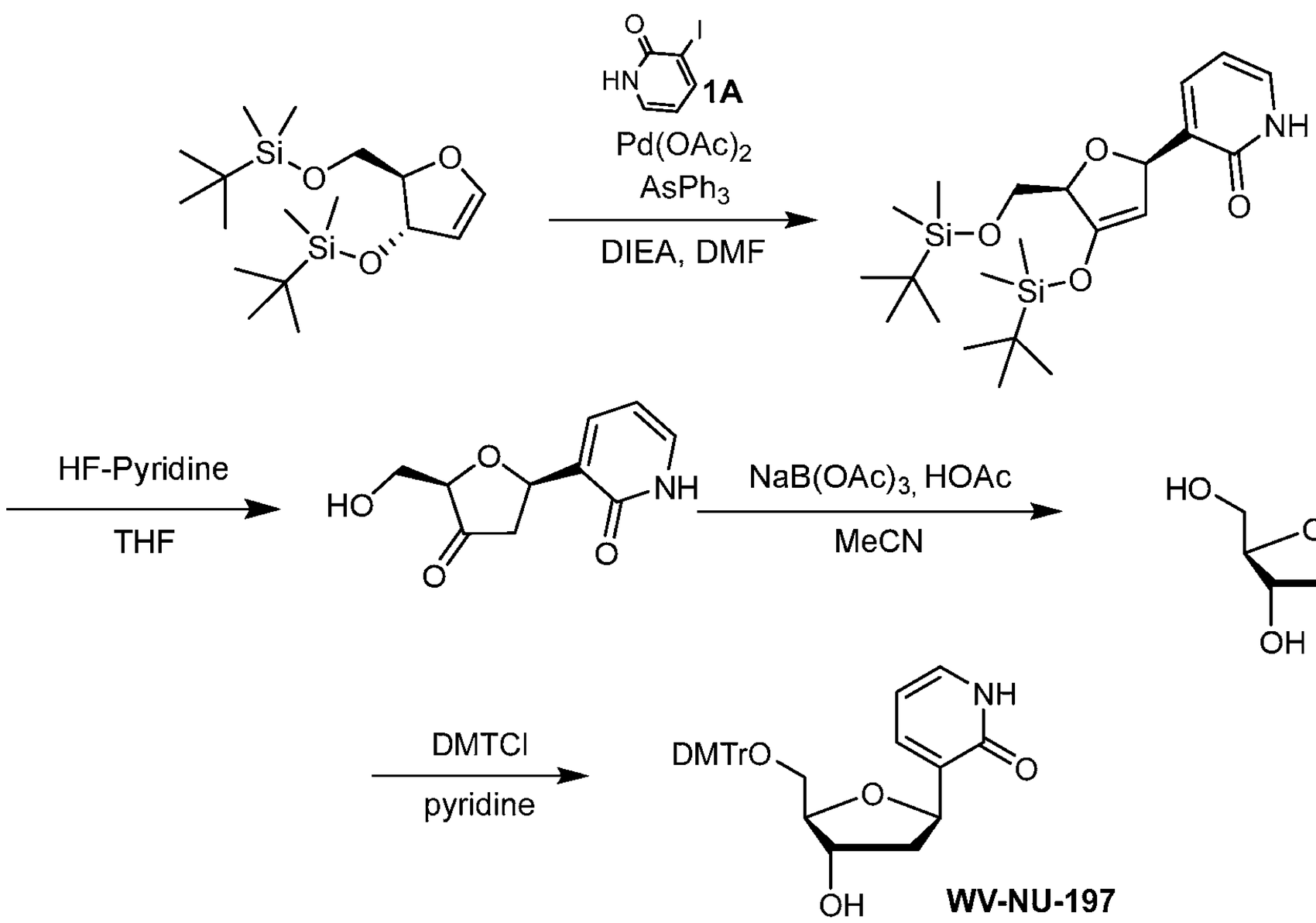
[001170] **Step 2**. To a solution of N-(5-((2R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (23 g, 46.39 mmol, 1 eq.) was added dropwise to a solution of pyridine : hydrofluoride (23.65 g, 167.02 mmol, 21.50 mL, 70% purity, 3.6 eq.) in THF (200 mL). The reaction was stirred at 25 °C for 12 hr. The suspension was diluted with acetic acid (30 mL) and the volatiles removed under reduced pressure. N-(5-((2R,5R)-5-(hydroxymethyl)-4-oxotetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (12.40 g, 46.40 mmol, 100.00% yield) was obtained as a white solid, which was used in the next step without further purification; LCMS (M+H+): 268.3.

[001171] **Step 3**. N-(5-((2R,5R)-5-(hydroxymethyl)-4-oxotetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (12.4 g, 46.40 mmol, 1 eq.) was dissolved in a mixture of MeCN (66 mL) /AcOH (66 mL) (1:1 v/ v,) and the mixture was cooled to -15 °C, followed by the portionwise addition of $NaBH(OAc)_3$ (23.11 g, 109.04 mmol, 2.35 eq.). The mixture was stirred at-15 °C for 2 hr. The mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100/1 to 5/1) to give N-(5-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (11 g, 40.85 mmol,

88.05% yield) as a white solid.

[001172] **Step 4**. To a solution of N-(5-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide (9 g, 33.43 mmol, 1 eq.) in pyridine (100 mL) was added DMTCl (11.33 g, 33.43 mmol, 1 eq.). The mixture was stirred at 15 °C for 12 hr. The residue was diluted with H_2O 200 mL and extracted with EtOAc 1500 mL (500mL * 3). The combined organic layers were washed with brine 30 mL (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100/1 to 5/1) to give **WV-NU-189** (15 g, 26.24 mmol, 78.51% yield) as a white solid. ^{1}HNMR (CHLOROFORM-d, 400MHz): δ = 7.94 (br s, 1H), 7.43 (br d, J = 7.3 Hz, 2H), 7.27 (s, 7H), 7.22 (br d, J = 6.8 Hz, 1H), 6.83 (br d, J = 8.8 Hz, 4H), 5.17 (br s, 1H), 4.40 (br s, 1H), 4.03 (br s, 1H), 3.78 (s, 6H), 3.21-3.36 (m, 2H), 2.48 (br s, 1H), 2.18 (br s, 3H), 1.95 ppm (br s, 1H); LCMS (M-H+): 570.3, LCMS purity: 91.61%.

[001173] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyridin-2(1H)-one (WV-NU-197)



[001174] **Step 1**. To a solution of BSA (18.30 g, 89.95 mmol, 22.23 mL, 3.1 eq.) was added dropwise to a suspension of 3-iodopyridin-2(1H)-one (16.03 g, 72.54 mmol, 2.5 eq.) in DMF (100 mL) under an argon atmosphere. After stirring for 1 h the reaction become a clear solution. Then DIEA (11.63 g, 89.95 mmol, 15.67 mL, 3.1 eq.) and tert-butyl(((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)dimethylsilane (10 g, 29.02 mmol, 1 eq.) were added. In a separate flask, $Pd(OAc)_2$ (456.01 mg, 2.03 mmol, 0.07 eq.) was added to a solution of triphenylarsane (3.55 g, 11.61 mmol, 0.4 eq.) in stirring DMF (100 mL). After 30 min, this solution was added slowly to the first flask and the mixture was stirred for 12 hr at 80 °C. The reaction was quenched with the addition of H_2O (300 mL) and the solvent was evaporated under

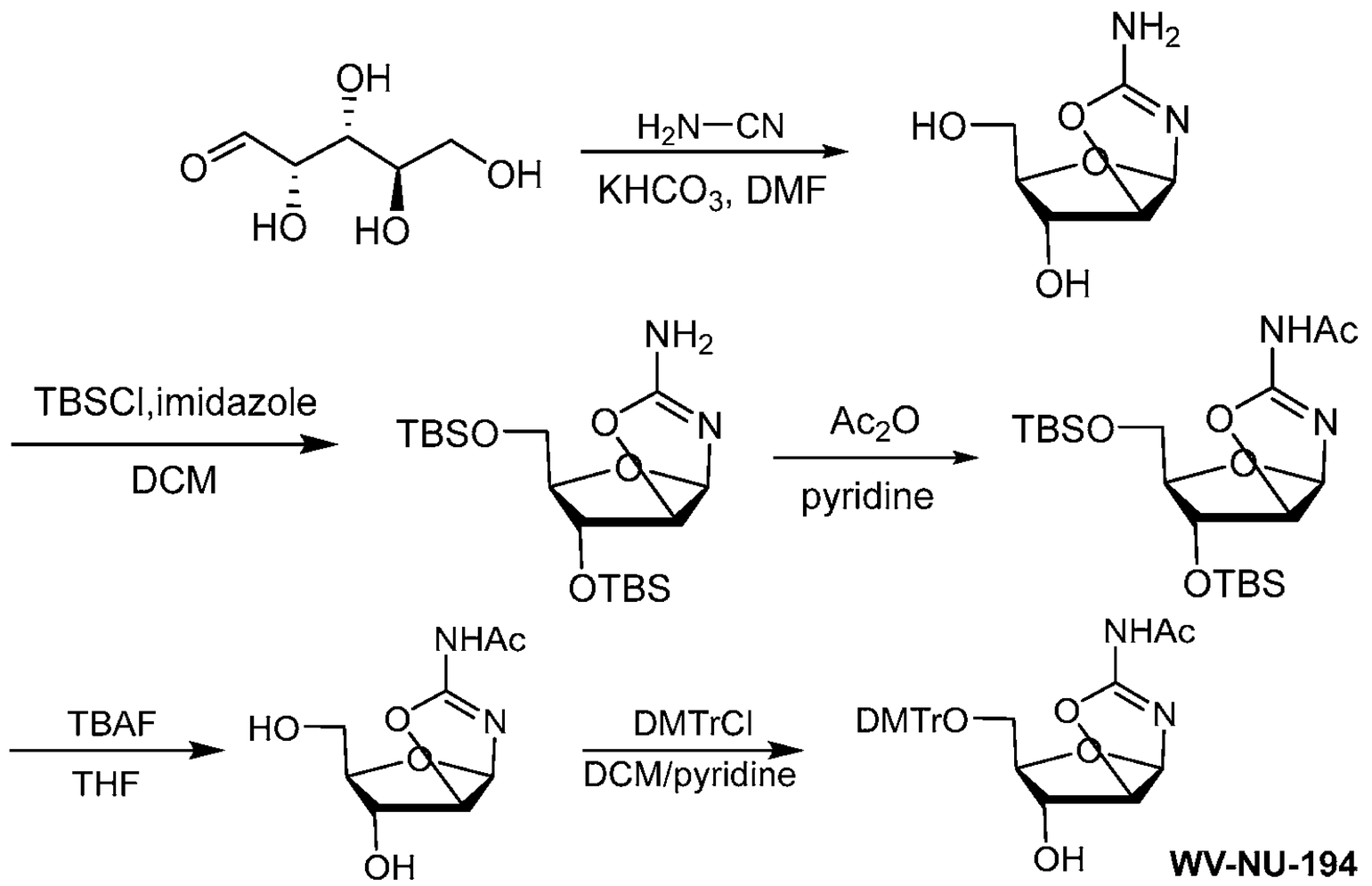
reduced pressure. The residue was redissolved in EtOAc (300mL), and washed with H_2O (2*100mL) and brine (30mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to give 3-((2R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-yl)pyridin-2(1H)-one (12 g, 27.41 mmol, 94.48% yield) as a white solid. ^{1}HNMR (CHLOROFORM-d, 400MHz): δ^1 = 12.66 (brs, 1H), 7.81-7.85 (m, 1H), 7.22-7.29 (m, 2H), 6.22 (t, J = 6.7 Hz, 1H), 5.86 (d, J = 3.3 Hz, 1H), 4.95 (t, J = 1.6 Hz, 1H), 4.49-4.59 (m, 1H), 3.85 (dd, J = 11.3, 2.1 Hz, 1H), 3.69 (dd, J = 11.2, 3.7 Hz, 1H), 0.78-0.90 (m, 17H), 0.14 (d, J = 16.4 Hz, 6H), -0.01 ppm (d, J = 8.6 Hz, 6H); LCMS: M+H$^+$ = 438.7.

[001175] Step 2. To a solution of 3-((2R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-yl)pyridin-2(1H)-one (12 g, 27.41 mmol, 1 eq.) in THF (120 mL) was added pyridine;hydrofluoride (11.89 g, 95.95 mmol, 10.81 mL, 80% purity, 3.5 eq.) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 15 °C for 12 hr under N_2 atmosphere. The filtration was concentrated in vacuum to give crude 3-((2R,5R)-5-(hydroxymethyl)-4-oxotetrahydrofuran-2-yl)pyridin-2(1H)-one (5.74 g, 27.44 mmol, 100.00% yield). LCMS: M+H$^+$ = 210.1 and M+Na$^+$ = 232.1.

[001176] Step 3. To a solution of 3-((2R,5R)-5-(hydroxymethyl)-4-oxotetrahydrofuran-2-yl)pyridin-2(1H)-one (5.74 g, 27.44 mmol, 1 eq.) was dissolved in a mixture of MeCN (70 mL)/AcOH (70 mL), followed by the portionwise addition of $NaBH(OAc)_3$ (13.67 g, 64.48 mmol, 2.35 eq.). The mixture was stirred at 15 °C for 2 hr. The mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=100/1 to 5/1) to give 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyridin-2(1H)-one (3.1 g, 14.68 mmol, 53.49% yield) as a white solid. ^{1}H NMR (CHLOROFORM-d, 400MHz): δ^1 = 7.72-7.78 (m, 1H), 7.35 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.40 (t, *J* = 6.7 Hz, 1H), 5.16 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.26-4.33 (m, 1H), 3.94 (td, *J* = 4.4, 2.7 Hz, 1H), 3.61-3.72 (m, 2H), 2.33 (ddd, *J* = 13.0, 5.9, 2.0 Hz, 1H), 1.87-2.00 ppm (m, 1H); LCMS: (M+H$^+$): 212.

[001177] Step 4. To a solution of 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyridin-2(1H)-one (3.10 g, 14.68 mmol, 1 eq.) in pyridine (30 mL) was added DMTrCl (4.48 g, 13.21 mmol, 0.9 eq.). The mixture was stirred at 15 °C for 2 hrs. The reaction mixture was diluted with H_20 50 mL and extracted with EAOAC 180 mL (60 mL * 3). The combined organic layers were washed with brine 15 mL (5 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100:1 to 5:1) to give **WV-NU-197** (5.2 g) as a white solid. ^{1}HNMR (DMSO-d6, 400MHz): δ^1 = 11.59 (br s, 1H), 7.39-7.50 (m, 3H), 7.18-7.35 (m, 8H), 6.89 (d, J = 8.5 Hz, 4H), 6.15 (t, J = 6.7 Hz, 1H), 5.06 (d, J = 4.1 Hz, 1H), 5.00 (dd, J = 9.2, 6.0 Hz, 1H), 4.00-4.16 (m, 1H), 3.82-3.95 (m, 1H), 3.73 (s, 6H), 2.99-3.17 (m, 3H), 2.26 (ddd, J = 12.7, 6.0, 2.5 Hz, 1H), 1.58 ppm (ddd, J = 12.7, 9.3, 6.1 Hz, 1H); LCMS: M+H$^+$: 513.6, LCMS purity 100.0%

[001178] Synthesis of N-((3aR,5R,6R,6aS)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-6-hydroxy-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide (WV-NU-194)



WV-NU-194

[001179] **Step 1**. A mixture of (2S,3R,4R)-2,3,4,5-tetrahydroxypentanal (80 g, 532.87 mmol, 1 eq.) in DMF (500 mL) and added $KHCO_3$ (2.80 g, 27.97 mmol, 5.25e-2 eq.) and NH_2CN (26.80 g, 637.49 mmol, 26.80 mL, 1.20 eq.) was stirred at 90°C for 1hr. After cooling to room temperature, the mixture was evaporated under reduced pressure to half volume and the resulting solution was stored for 20hr at 5°C. The precipitate obtained was filtered off and recrystallized from 96% aq. EtOH (600ml) to give (3aR,5R,6R,6aS)-2-amino-5-(hydroxymethyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-6-ol (50 g) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 6.36 (br s, 2H), 5.66 (d, J = 5.6 Hz, 1H), 5.46 (br s, 1H), 4.75 (br s, 1H), 4.53 (br d, J = 5.5 Hz, 1H), 4.00 (br s, 1H), 3.67 - 3.59 (m, 1H), 3.40 (s, 1H), 3.33 - 3.19 (m, 2H).

[001180] **Step 2.** To a solution of (3aR,5R,6R,6aS)-2-amino-5-(hydroxymethyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-6-ol (20 g, 114.84 mmol, 1 eq.) in DCM (200 mL) was added imidazole (46.91 g, 689.04 mmol, 6 eq.), and then added TBSCl (60.58 g, 401.94 mmol, 49.25 mL, 3.5 eq.). The mixture was stirred at 30°C for 10hr. The reaction mixture of two batches were filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate: Methanol = 0:1 to 5:1) to give (3aR,5R,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-amine (91 g, 135.59 mmol, 55.15% yield, 60% purity) as a white solid. ^{1}HNMR (400 MHz, CHLOROFORM-d) δ = 5.87 (d, J = 5.6 Hz, 1H), 4.64 (d, J = 5.6 Hz, 1H), 4.32 (d, J = 2.5 Hz, 1H), 3.91 - 3.81 (m, 1H), 3.63 (dd, J = 5.1, 10.7 Hz, 1H), 3.46 (dd, J = 7.6, 10.6 Hz, 1H), 0.91 - 0.86 (m, 19H), 0.11 (d, J = 8.0 Hz, 6H), 0.03 (s, 6H); **LCMS (M+H$^+$)**: 403.3, purity: 79.78%.

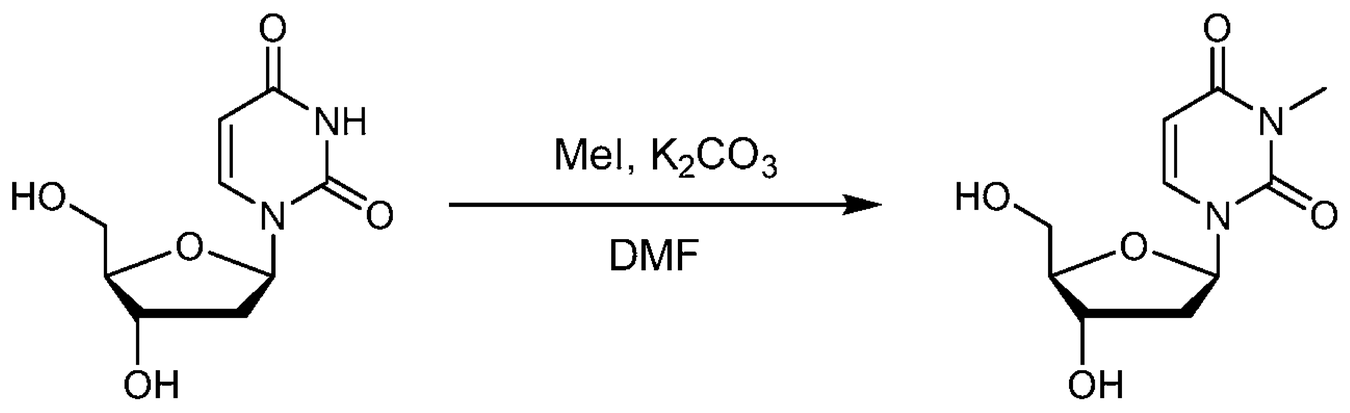
[001181] **Step 3**. To a mixture solution of (3aR,5R,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-amine (40 g, 99.34 mmol, 1 *eq.*) in PYRIDABEN (400 mL) was by drops added Ac_2O (7.10 g, 69.54 mmol, 6.51 mL, 0.7 *eq.*). The mixture was stirred at 25°C for 12hr. The reaction mixture was filtered and concentrated under reduced pressure to give a

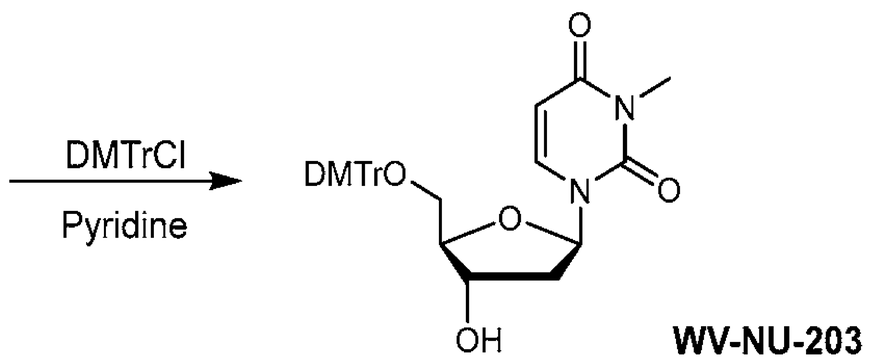
residue. The residue was purified by column chromatography (SiO2, Petroleum ether: Ethyl acetate = 50:1 to 15:1) to give N-((3aR,5R,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide (33 g, 74.21 mmol, 74.70% yield) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.91 (d, J = 5.8 Hz, 1H), 4.81 (dd, J = 1.0, 5.8 Hz, 1H), 4.49 (dd, J = 0.9, 2.8 Hz, 1H), 3.98 (ddd, J = 2.9, 4.8, 7.4 Hz, 1H), 3.61 (dd, J = 5.0, 10.9 Hz, 1H), 3.44 (dd, J = 7.4, 10.9 Hz, 1H), 2.16 (s, 3H), 0.90 - 0.88 (m, 9H), 0.87 - 0.85 (m, 9H), 0.12 (d, J = 9.6 Hz, 6H), 0.02 (d, J = 3.8 Hz, 6H); LCMS $(M+H)^+$: 445.4, purity: 92.67%.

[001182] Step 4. To a solution of N-((3aR,5R,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide (33 g, 74.21 mmol, 1 eq.) in THF (300 mL) was added TBAF (1 M, 111.31 mL, 1.5 eq.). The mixture was stirred at 25°C for 1hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: C18 20-35um 100A 100g; mobile phase: [water-ACN]; B%: 0%-0% @ 30mL/min), after purification see LCMS (ET35599-347-P2A1) to give N-((3aR,5R,6R,6aS)-6-hydroxy-5-(hydroxymethyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide (11 g, 50.88 mmol, 68.75% yield) as a white solid. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ = 4.43 - 4.36 (m, 1H), 4.14 - 3.98 (m, 3H), 3.84 - 3.61 (m, 3H), 3.56 (dd, J = 4.8, 12.4 Hz, 1H), 3.49 - 3.41 (m, 1H), 2.09 (s, 3H); LCMS $(M+H^+)$: 217.2, purity: 99.41%.

[001183] Step 5. To a solution of N-((3aR,5R,6R,6aS)-6-hydroxy-5-(hydroxymethyl)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide (10 g, 46.26 mmol, 1 eq.) in DCM (50 mL) was added PYRIDINE (7.32 g, 92.51 mmol, 7.47 mL, 2 eq.) and DMTrCl (9.40 g, 27.75 mmol, 0.6 eq.) at 0°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was quenched by addition water 200 mL, and then extracted with DCM (200mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: C18 20-35um 100A 100g; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 40%-65%, 20min to give **WV-NU-194** (5.1 g, 9.83 mmol, 21.26% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.60 (br s, 1H), 7.37 (d, J = 7.5 Hz, 2H), 7.29 - 7.19 (m, 7H), 7.16 - 7.10 (m, 1H), 6.75 (dd, J = 4.4, 8.8 Hz, 4H), 5.89 (d, J = 6.0 Hz, 1H), 4.96 (dd, J = 1.6, 5.9 Hz, 1H), 4.42 (br d, J = 4.9 Hz, 1H), 4.11 - 4.06 (m, 1H), 3.74 (d, J = 2.1 Hz, 6H), 3.29 - 3.19 (m, 2H), 2.01 (s, 3H); LCMS $(M-H^+)$:517, purity: 100%.

[001184] Synthesis of 1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-3-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-203)



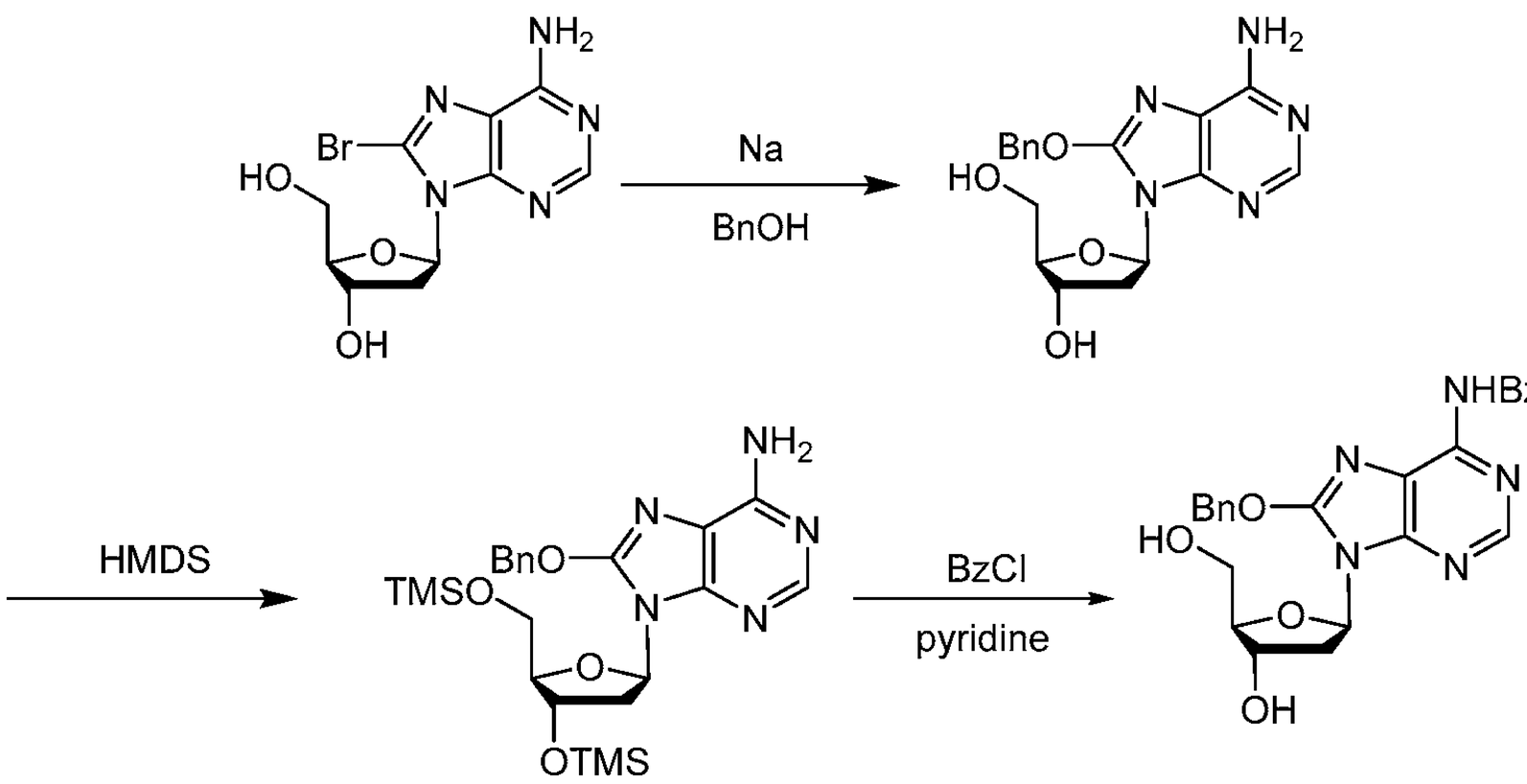


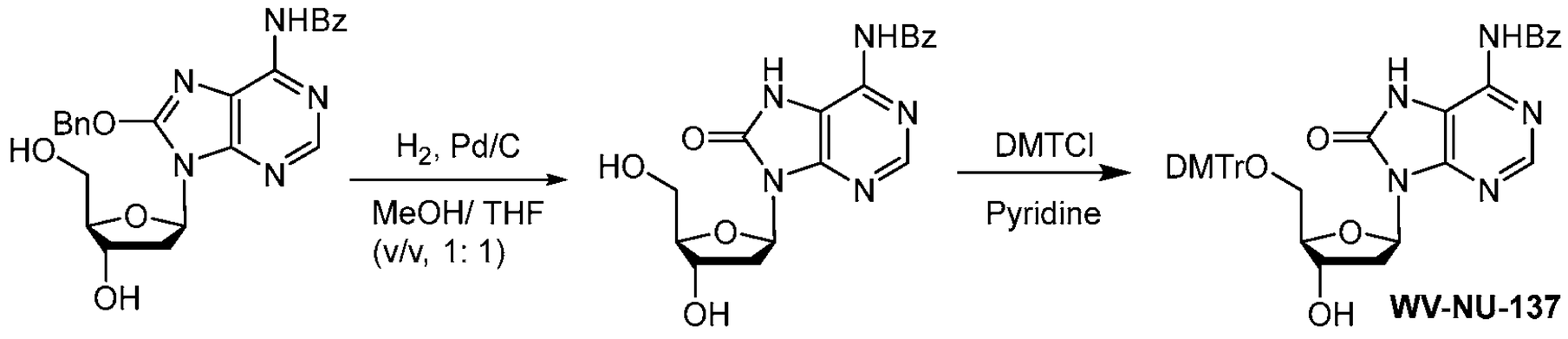
WV-NU-203

[001185] Step 1. To a solution of 1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (20 g, 87.64 mmol, 1 *eq.*) in DMF (200 mL) was added MeI (31.10 g, 219.10 mmol, 13.64 mL, 2.5 *eq.*) and K_2CO_3 (36.34 g, 262.93 mmol, 3 *eq.*). The mixture was stirred at 55 °C for 2 hr. The reaction mixture was filtered, and filter liquor was concentrated under reduced pressure to give a residue, and then extracted with DCM 200 mL * 2. The combined organic layers were dried over, filtered and concentrated under reduced pressure to give 1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-methylpyrimidine-2,4(1H,3H)-dione (15 g) as a white solid. LCMS: ($M+H^+$) 243.2.

[001186] Step 2. To a solution of 1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-methylpyrimidine-2,4(1H,3H)-dione (15 g, 61.93 mmol, 1 *eq.*) in Pyridine (150 mL) was added DMTCl (23.08 g, 68.12 mmol, 1.1 *eq.*). The mixture was stirred at 15 °C for 1 hr. The reaction mixture was extracted with ethyl acetate 150mL * 2. The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give WV-NU-203 (13 g, 23.87 mmol, 38.55% yield) as a yellow solid. ^{1}HNMR (400MHz, DMSO-d_6) δ = 7.42 - 7.34 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.26 - 7.18 (m, 5H), 6.92 - 6.84 (m, 4H), 5.56 - 5.45 (m, 1H), 5.39 - 5.29 (m, 1H), 4.34 - 4.23 (m, 1H), 3.79 - 3.69 (m, 6H), 3.37 - 3.25 (m, 5H), 3.18 - 3.11 (m, 3H), 2.25 - 2.16 (m, 2H); LCMS: purity: 92.72%, ($M - H^+$):543.59.

[001187] Synthesis of N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (WV-NU-137)





[001188] **Step 1.** A solution of Na (9.99 g, 434.67 mmol) in BnOH (391.84 g, 3.62 mol), 3 hr later, (2R,3S,5R)-5-(6-amino-8-bromo-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (25 g, 75.73 mmol) was added. The mixture was stirred at 15 °C for 12 hr. The reaction mixture was quenched by addition HCl (1M) 800 mL at 0°C, then added sat. $NaHCO_3$ aq. until pH~9, and extracted with EtOAc (1000 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ((SiO_2, Petroleum ether/Ethyl acetate = 5/1 to Ethyl acetate : Methanol = 10/1) to get (2R,3S,5R)-5-(6-amino-8-(benzyloxy)-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (35 g, 64.67% yield) was obtained as a yellow oil. LCMS: (M+H+): 358.2

[001189] **Step 2.** (2R,3S,5R)-5-(6-amino-8-(benzyloxy)-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (50 g, 139.91 mmol) (dried by azeotropic distillation on a rotary evaporator with pyridine (200 mL*3)) was added HMDS (338.72 g, 2.10 mol). The mixture was stirred at 150 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. 8-(benzyloxy)-9-((2R,4S,5R)-4-((trimethylsilyl)oxy)-5-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-9H-purin-6-amine (70.2 g, crude) was obtained as a yellow oil without purification.

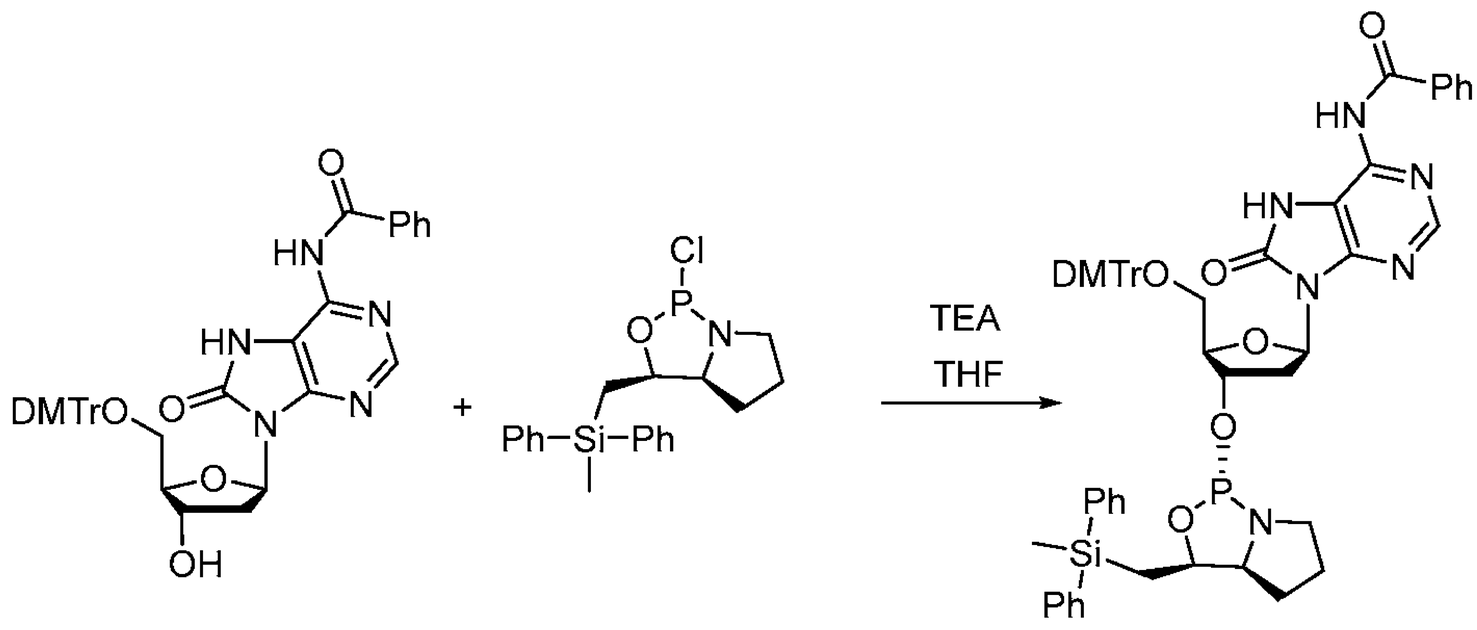
[001190] **Step 3.** To a solution of 8-(benzyloxy)-9-((2R,4S,5R)-4-((trimethylsilyl)oxy)-5-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-9H-purin-6-amine (70.2 g) in PYRIDINE (500 mL) was added BzCl (29.50 g). The mixture was stirred at 20°C for 2hr. MeOH (500 mL) and water (500 mL) was added, 10 min later $NH_3.H_2O$ (250mL) was added, 30 min later H_2O (500 mL) was added and extracted with EtOAc (500 mL * 4). dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1, then ethyl acetate/methanol = 10:1) to get N-(8-(benzyloxy)-9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (36 g, 55.76% yield) as a yellow solid. LCMS: (M+H+): 462.2

[001191] **Step 4.** To a solution of N-(8-(benzyloxy)-9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (36 g, 78 mmol) in THF (500 mL) and MeOH (500 mL) was added Pd/C (9 g, 39.01 mmol, 10% purity). The mixture was stirred at 15 °C for 3 hr in H_2 (15 psi). The mixture was filtered, and the filtrated was concentrated under the reduced pressure to get N-(9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (28.9 g, crude) as a yellow solid. LCMS: (M+H+): 372.2.

Step 5. To a solution of N-(9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (28.9 g, 77.82 mmol) in PYRIDINE (300 mL) was added DMTCl (26.37

g, 77.82 mmol), the mixture was stirred at 15°C for 12 hr. The reaction mixture was quenched by addition water (200 mL) at 0 °C, and extracted with EtOAc (300 mL * 3). Dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 10/1, 1/4, 5%TEA) to get N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide **(WV-NU-137)** (32 g, 57.75% yield) as a white solid. ^{1}HNMR (400MHz, 400MHz, DMSO-d6) δ = 8.38 - 8.24 (m, 1H), 8.12 - 8.00 (m, 2H), 7.67 - 7.60 (m, 1H), 7.58 - 7.51 (m, 2H), 7.38 - 7.33 (m, 2H), 7.26 - 7.13 (m, 7H), 6.81 (dd, J = 9.0, 13.3 Hz, 4H), 6.25 (t, J = 6.8 Hz, 1H), 5.29 (d, J = 4.6 Hz, 1H), 4.56 - 4.49 (m, 1H), 3.95 (q, J = 4.9 Hz, 1H), 3.71 (d, J = 4.4 Hz, 6H), 3.20 - 3.15 (m, 2H), 3.08 (td, J = 6.5, 13.0 Hz, 1H), 2.21 - 2.10 (m, 1H); LCMS (M-H$^+$): 672.2.

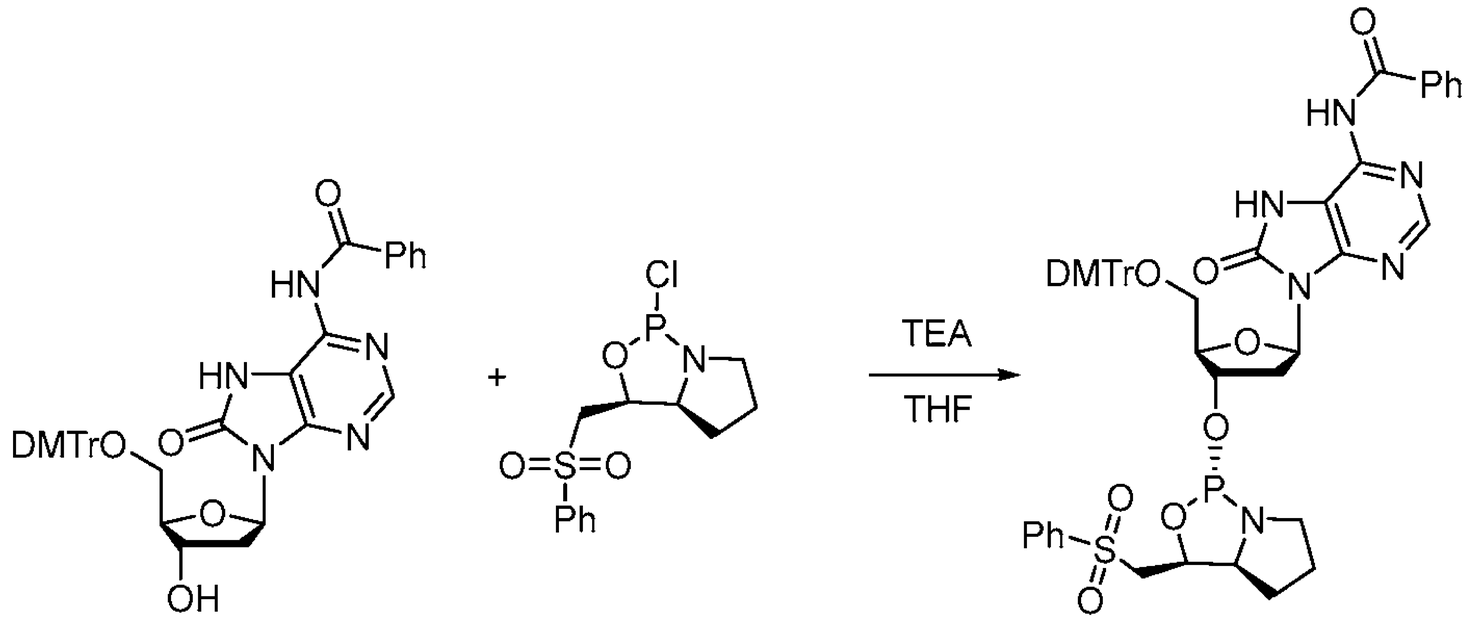
[001192] Synthesis of N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide



[001193] Dry N-[9-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-8-oxo-7H-purin-6-yl]benzamide (4.0 g, 5.94 mmol) in a rbf was dissolved in THF (50 mL). To the clear solution was added triethylamine (5.59 mL, 40.08 mmol). [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.96*M* solution in THF, 11.16 mL, 10.69 mmol) was added dropwise. The reaction solution was stirred at rt for 2 hr. TLC showed the reaction was complete. Anhydrous MgSO4 (708 mg) was added. Stirred for 1 min. The mixture was filtered, and the filtrate was concentrated. The resulting crude product was purified by normal phase column chromatography applying 0-100% EtOAc in hexanes (each mobile phase contained 1.5% triethylamine) as the gradient to afford N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide as a white foam (4.45 g, 74.0% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.59 (s, 1H), 8.17 (s, 1H), 7.98 – 7.93 (m, 2H), 7.68 – 7.62 (m, 1H), 7.58 – 7.53 (m, 2H), 7.53 – 7.46 (m, 4H), 7.45 – 7.40 (m, 2H), 7.33 – 7.26 (m, 7H), 7.24 – 7.17 (m, 5H), 7.16 – 7.11 (m, 1H), 6.76 – 6.69 (m, 4H), 6.30 (dd, J = 7.3, 6.1 Hz, 1H), 5.05 (ddt, J = 8.9, 6.9, 4.5 Hz, 1H), 4.85 (dt, J = 8.9, 5.7 Hz, 1H), 4.03 (q, J = 5.0 Hz, 1H), 3.73 (d, J = 4.5 Hz, 6H), 3.49 (ddt, J = 14.6, 10.6,

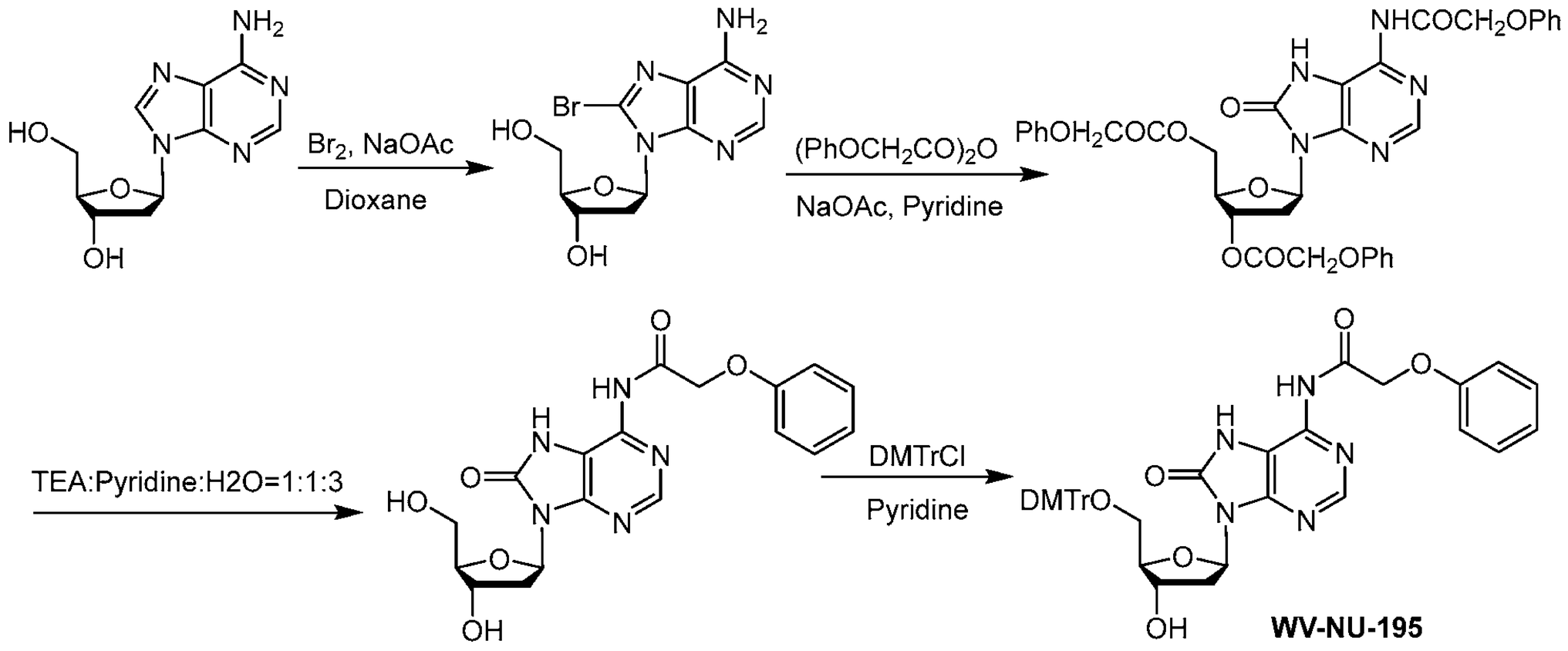
7.6 Hz, 1H), 3.40 (ddt, J = 12.6, 7.0, 5.5 Hz, 1H), 3.34 (dd, J = 10.1, 4.9 Hz, 1H), 3.25 (dd, J = 10.1, 5.9 Hz, 1H), 2.97 (tdd, J = 10.8, 8.8, 4.3 Hz, 1H), 2.83 (dt, J = 13.3, 6.6 Hz, 1H), 2.08 (ddd, J = 13.5, 7.4, 4.6 Hz, 1H), 1.84 (ddt, J = 12.2, 8.5, 4.3 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.55 (dd, J = 14.7, 8.9 Hz, 1H), 1.45 – 1.38 (m, 2H), 1.30 – 1.20 (m, 1H), 0.65 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 148.40; MS (ESI), 1013.18 $[M + H]^+$.

[001194] Synthesis of N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide



[001195] To a solution of dry N-[9-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-8-oxo-7H-purin-6-yl]benzamide (3.0 g, 4.45 mmol) in THF (30 mL) was added triethylamine (1.55 mL, 11.13 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.9*M* in THF, 8.91 mL, 8.02 mmol) was added dropwise. The resulting off-white slurry was stirred at rt for 2 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (80 uL). Anhydrous MgSO4 (1.07 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 2.5% triethylamine) as the gradient to afford the title compound as a white foam (2.979 g, 69.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.60 (s, 1H), 8.24 (s, 1H), 7.97 – 7.92 (m, 2H), 7.92 – 7.88 (m, 2H), 7.67 – 7.62 (m, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.48 (m, 4H), 7.45 – 7.40 (m, 2H), 7.34 – 7.28 (m, 4H), 7.21 (dd, J = 8.3, 6.7 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.79 – 6.72 (m, 4H), 6.39 (t, J = 6.8 Hz, 1H), 5.09 (ddt, J = 14.7, 6.9, 4.9 Hz, 2H), 4.08 – 4.03 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.69 (dq, J = 9.8, 5.9 Hz, 1H), 3.52 – 3.42 (m, 2H), 3.37 (ddd, J = 12.2, 5.4, 2.4 Hz, 2H), 3.34 – 3.24 (m, 2H), 3.03 (tdd, J = 10.3, 8.8, 4.1 Hz, 1H), 2.30 (ddd, J = 13.5, 7.3, 4.5 Hz, 1H), 1.87 (dt, J = 11.4, 5.9 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.70 – 1.63 (m, 1H), 1.12 (dtd, J = 11.7, 10.1, 8.5 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 149.85; MS (ESI), 955.37 $[M - H]^-$.

[001196] Synthesis of N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)-2-phenoxyacetamide (WV-NU-195)



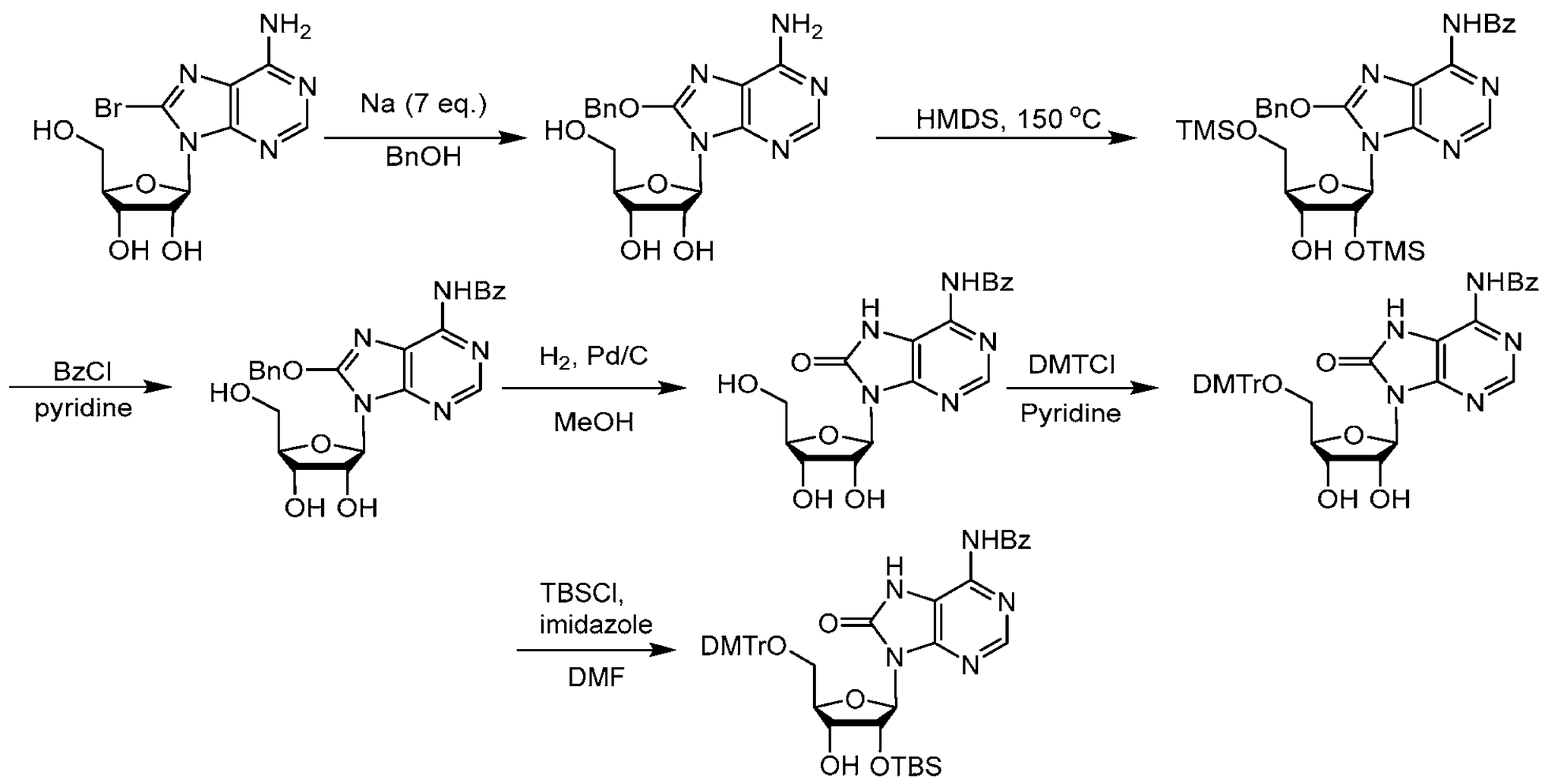
[001197] Step 1. For three batches: To a soln. of (2R,3S,5R)-5-(6-amino-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (30 g, 119.41 mmol, 1 *eq.*) in dioxane (400 mL) and AcONa (0.5 M, 480 mL, 2.01 *eq.*) buffer (pH 4.7), a solution of Br_2 (22.90 g, 143.29 mmol, 7.39 mL, 1.2 *eq.*) in dioxane (500 mL) was added dropwise while stirring. The mixture was stirred at 15°C for 12h. The three batches were combined for work up. To the mixture conc.$Na_2S_2O_5$ was added until the red color vanished. The mixture was neutralized to pH 7.0 with 0.5 M NaOH. The residue was evaporated, when a white solid precipitated. The solid was filtered off, washed with cold 1,4-dioxane (50 mL), and dried under high vacuum to give (2R,3S,5R)-5-(6-amino-8-bromo-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (100 g, 302.90 mmol, 84.56% yield) as a yellow solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 8.22 - 7.98 (m, 1H), 7.53 (br s, 2H), 6.29 (dd, J=6.5, 7.9 Hz, 1H), 5.35 (br d, J=12.3 Hz, 2H), 4.58 - 4.38 (m, 1H), 3.95 - 3.82 (m, 1H), 3.65 (dd, J=4.5, 11.9 Hz, 1H), 3.48 (br dd, J=4.5, 11.7 Hz, 1H), 3.36 (br s, 1H), 3.24 (ddd, J=6.1, 7.8, 13.4 Hz, 1H), 2.19 (ddd, J=2.6, 6.4, 13.1 Hz, 1H); LCMS (M+H+): 330.1.

[001198] Step 2. To a solution of (2R,3S,5R)-5-(6-amino-8-bromo-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (55 g, 166.60 mmol, 1 *eq.*) in Pyridine (1500 mL) was added NaOAc (24.87 g, 303.21 mmol, 1.82 *eq.*) and (2-phenoxyacetyl) 2-phenoxyacetate (267.08 g, 932.94 mmol, 5.6 *eq.*). The mixture was stirred at 80°C for 2 hr. The reaction mixture was quenched by addition H_2O 100 mL and the mixture left at r.t. for 10 min. The mixture was evaporated and then diluted with DCM 1000 mL and sat. $NaHCO_3$ 1000 mL, extracted with DCM (1000 mL * 2). The combined organic layers were washed with brine (1000 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/ (DCM/ EtOAc = 1:1) = 1/0 to 0/1), then some solid was precipitate out on the column, washed the column with DCM 2 L and concentrated to get a crude. The crude product was triturated with methanol 1000 mL. (2R,3S,5R)-5-(8-oxo-6-(2-phenoxyacetamido)-7,8-dihydro-9H-purin-9-yl)-2-((2-phenoxyacetoxy)methyl)tetrahydrofuran-3-yl 2-phenoxyacetate (60 g, 67.20 mmol, 40.34% yield, 75% purity) was obtained as a brown solid. LCMS ($M-H^+$): 668.2.

[001199] **Step 3**. For two batches: To a solution of (2R,3S,5R)-5-(8-oxo-6-(2-phenoxyacetamido)-7,8-dihydro-9H-purin-9-yl)-2-((2-phenoxyacetoxy)methyl)tetrahydrofuran-3-yl 2-phenoxyacetate (27 g, 40.32 mmol, 1 *eq.*) in the mixture solvent of TEA (270 mL), PYRIDINE (270 mL) and H_2O (810 mL). The mixture was stirred at 15 °C for 1.5 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude of two batches were combined and purified by re-crystallization from methanol 500 mL to give N-(9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)-2-phenoxyacetamide (18 g, 44.85 mmol, 55.61% yield) as a brown solid. LCMS ($M-H^+$): 400.1.

[001200] **Step 4**. To a solution of N-(9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)-2-phenoxyacetamide (16 g, 39.86 mmol, 1 *eq.*) in Pyridine (300 mL) was added DMTCl (18.91 g, 55.81 mmol, 1.4 *eq.*). The mixture was stirred at 15 °C for 10 hr. The reaction mixture was quenched by addition water 50 mL, and then diluted with sat. $NaHCO_3$ 500 mL and extracted with ethyl acetate 1500 mL (500 mL *3). The combined organic layers were washed with sat. brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1, 5% TEA) to give **WV-NU-195** (20 g, 27.63 mmol, 69.30% yield, 97.21 % purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.94 (br s, 1H), 10.50 (br s, 1H), 8.26 (s, 1H), 7.38 - 7.28 (m, 4H), 7.26 - 7.11 (m, 7H), 7.06 - 6.94 (m, 3H), 6.79 (dd, J = 8.9, 14.1 Hz, 4H), 6.23 (t, J = 6.8 Hz, 1H), 5.27 (d, J = 4.6 Hz, 1H), 4.84 (s, 2H), 4.58 - 4.44 (m, 1H), 3.97 - 3.91 (m, 1H), 3.70 (d, J = 5.0 Hz, 6H), 3.22 - 3.11 (m, 2H), 3.05 (td, J = 6.4, 13.0 Hz, 1H), 2.14 (ddd, J = 4.9, 7.6, 12.9 Hz, 1H); LCMS ($M-H^-$): 702.3; purity: 97.21%.

[001201] Synthesis of N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide



[001202] **Step 1.** To a solution of Na (21 g, 913.45 mmol, 21.65 mL, 8.43 eq.) in BnOH (1000 mL), 3hr

later, (2R,3R,4S,5R)-2-(6-amino-8-bromo-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (37.5 g, 108.34 mmol, 1.0 eq.) was added. The mixture was stirred at 15 °C for 12 hr. The mixture was poured into cold 1N HCl (2500 mL) and extracted with EtOAc (1500 mL). The aqueous phase was added sat.$NaHCO_3$ (aq) until pH > 8, and the white cake was separated out, filtered and concentrated to get the crude. (2R,3R,4S,5R)-2-(6-amino-8-(benzyloxy)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (80 g, crude) was obtained as white solid. LCMS: ($M+H^+$):374.4.

[001203] Step 2. To a solution of (2R,3R,4S,5R)-2-(6-amino-8-(benzyloxy)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (39.0 g, 104.46 mmol, 1.0 eq.) in HMDS (400 mL), the mixture was stirred at 130°C for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The N-(8-(benzyloxy)-9-((2R,3R,4R,5R)-4-hydroxy-3-((trimethylsilyl)oxy)-5-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (61.62 g, crude) was obtained as brown solid.

[001204] Step 3. To a solution of N-(8-(benzyloxy)-9-((2R,3R,4R,5R)-4-hydroxy-3-((trimethylsilyl)oxy)-5-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (46.0 g, 77.98 mmol, 1 *eq.*) in pyridine (460 mL) was added benzoyl chloride (21.92 g, 155.96 mmol, 18.12 mL, 2.0 *eq.*). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was added MeOH : H_2O (1:1) 500 mL and stirred at 15°C for 10 mins. Then the mixture was added $NH_3.H_2O$ (150 mL) and stirred for 10 min at 15°C. Then the mixture was diluted by H_2O 200 mL and exacted by EtOAc 800 mL (200 mL*4). The mixture was added brine 200 mL and dried over Na_2SO_4. Then the mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography. N-(8-(benzyloxy)-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (33.99 g, 71.19mmol, 91.29% yield) was obtained as yellow solid. LCMS: ($M+H^+$): 478.4.

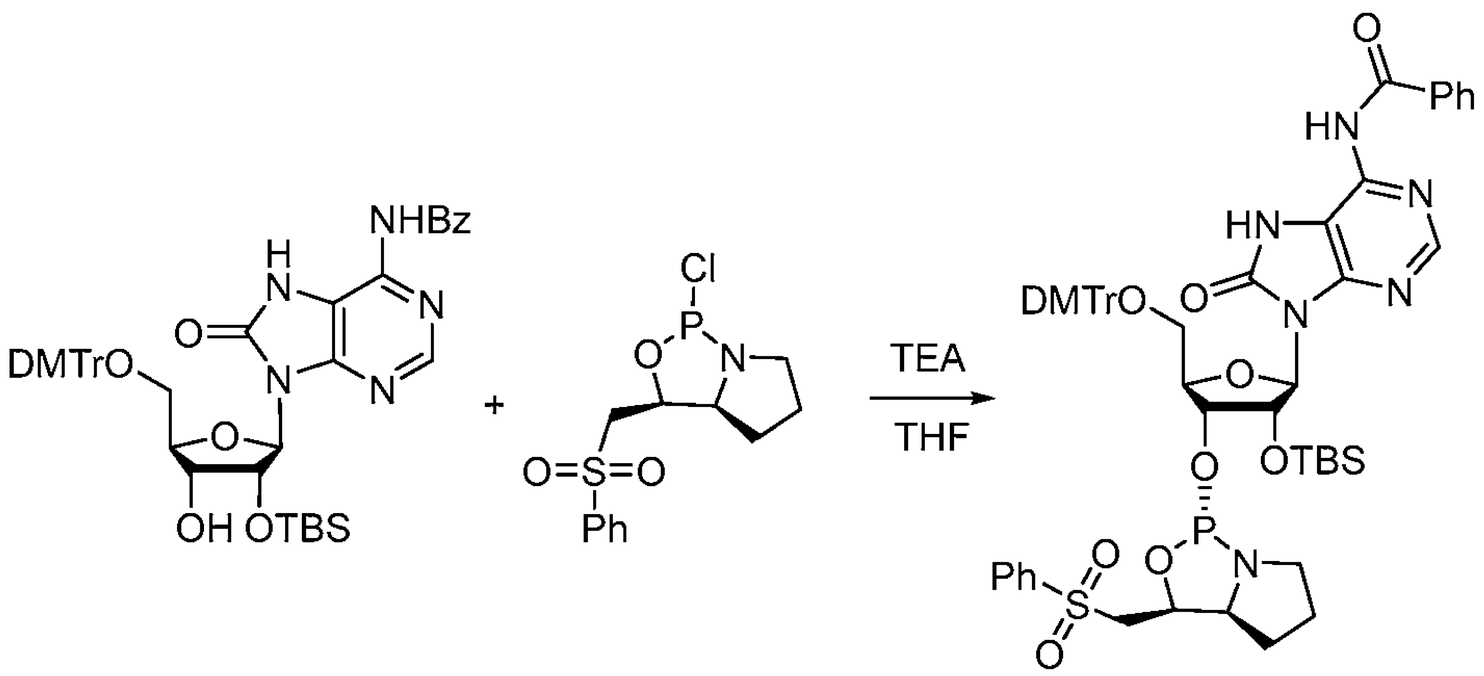
[001205] Step 4. To a solution of N-(8-(benzyloxy)-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (35.1 g, 73.51 mmol, 1 *eq.*) in MeOH (1500 mL) and THF (500 mL) was added Pd/C (7.0 g, 10% purity) under H_2 (15 psi). The mixture was stirred at 20°C for 1 hr. The reaction was filtered and concentrated under reduced pressure to give a residue. The residue was not purified and the N-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (19.6 g, 50.60 mmol, 68.83% yield) was obtained as brown solid. LCMS: ($M+H^+$):388.2.

[001206] Step 5. To a solution of N-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (14.8 g, 38.21 mmol, 1 *eq.*) in pyridine (150 mL) was added DMTCl (15.54 g, 45.85 mmol, 1.2 *eq.*). The mixture was stirred at 20°C for 2 hrs. The reaction mixture was diluted with H_2O 10 mL and extracted with ethyl acetate. The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Residue was purified by column chromatography (Petroleum ether/Ethyl acetate = 100/1 to 0/1). N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-

7H-purin-6-yl)benzamide (13.2 g, 19.14 mmol, 50.09% yield) was obtained as brown solid. LCMS: ($M+H^+$): 690.5.

[001207] Step 6. To a solution of N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (10.20 g, 14.79mmol, 1 *eq.*) in DMF (100 mL) was added imidazole (3.02 g, 44.37 mmol, 3.00 *eq.*) and TBSCl (2.01 g, 13.31 mmol, 1.63 mL, 0.9 *eq.*) . The mixture was stirred at 15°C for 10 hrs. The mixture was diluted with ethyl acetate and washed with $NaHCO_3$ solution. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1). N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide (3.82 g, 4.75 mmol, 32.13% yield) was obtained as yellow solid. ^{1}HNMR (400MHz, CHLOROFORM-d) δ = 9.51 (s, 1H), 8.57 (s, 1H), 8.26 (s, 1H), 8.03 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.70 - 7.63 (m, 1H), 7.61 - 7.54 (m, 2H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.36 (dd, *J* = 2.0, 8.9 Hz, 4H), 7.26 - 7.16 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 4H), 5.99 (d, *J* = 4.6 Hz, 1H), 5.32 - 5.27 (m, 1H), 4.48 (q, *J* = 5.5 Hz, 1H), 4.13 - 4.08 (m, 1H), 3.78 (s, 6H), 3.46 (dd, *J* = 3.9, 10.3 Hz, 1H), 3.32 (dd, *J* = 5.3, 10.3 Hz, 1H), 2.70 (d, *J* = 5.9 Hz, 1H), 2.06 (s, 1H), 1.58 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H); LCMS: ($M-H^-$):802.3.

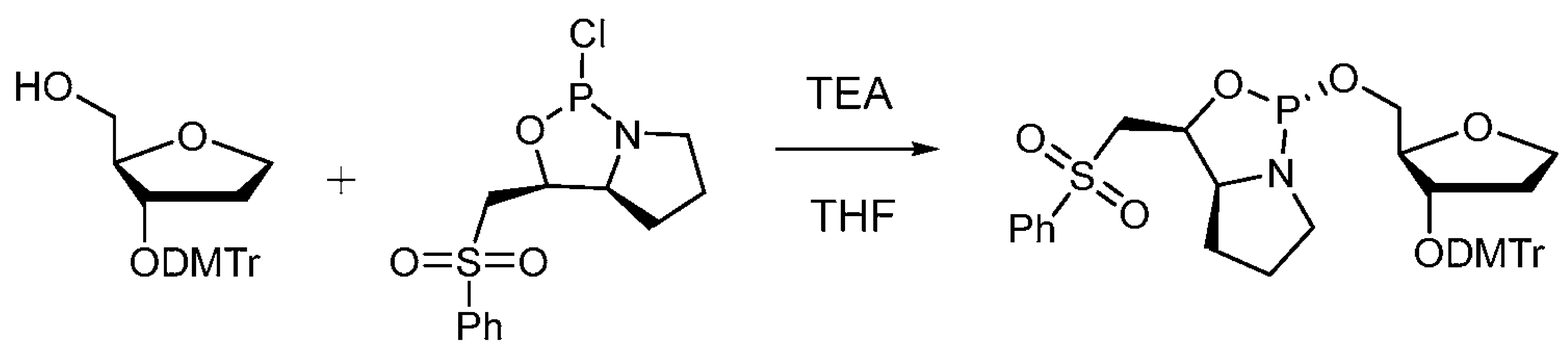
[001208] Synthesis of N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)benzamide



[001209] To a solution of dry N-[9-[(2R,3S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-3-[tert-butyl(dimethyl)silyl]oxy-4-hydroxy-tetrahydrofuran-2-yl]-8-oxo-7H-purin-6-yl]benzamide (3.5 g, 4.35 mmol) in THF (35 mL) was added triethylamine (1.52 mL, 10.88 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.9*M* in THF, 8.71 mL, 7.84 mmol) was added dropwise. The resulting cloudy solution was stirred at rt for 3.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (78 uL). Anhydrous

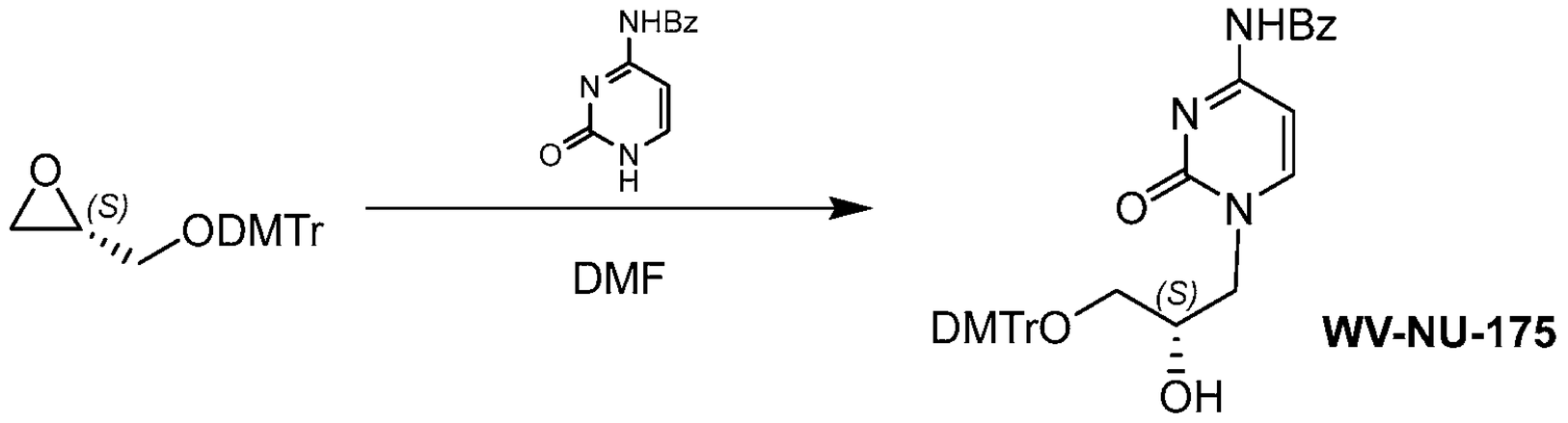
$MgSO_4$ (1.05 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 2.5% triethylamine) as the gradient to afford the title compound as a white foam (3.512 g, 74.2% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.62 (s, 1H), 8.24 (s, 1H), 7.96 – 7.92 (m, 2H), 7.90 – 7.85 (m, 2H), 7.67 – 7.61 (m, 1H), 7.57 (td, J = 7.2, 1.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.50 – 7.43 (m, 4H), 7.38 – 7.32 (m, 4H), 7.22 (dd, J = 8.4, 6.9 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.79 – 6.72 (m, 4H), 6.01 (d, J = 5.4 Hz, 1H), 5.33 (t, J = 5.3 Hz, 1H), 5.00 (q, J = 6.2 Hz, 1H), 4.78 (dt, J = 10.8, 4.7 Hz, 1H), 4.06 (q, J = 4.4 Hz, 1H), 3.76 (s, 6H), 3.67 (dq, J = 11.4, 5.8 Hz, 1H), 3.49 – 3.34 (m, 4H), 3.19 (dd, J = 10.4, 4.9 Hz, 1H), 3.01 (qd, J = 9.5, 4.0 Hz, 1H), 1.85 (t, J = 5.8 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.68 – 1.62 (m, 1H), 1.16 – 1.06 (m, 1H), 0.83 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 152.12; MS (ESI), 1086.13 $[M - H]^-$.

[001210] Synthesis of (1S,3S,3aS)-1-(((2R,3S)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)tetrahydrofuran-2-yl)methoxy)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole



[001211] To a white slurry of dry [(2R,3R)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]tetrahydrofuran-2-yl]methanol (10.0 g, 23.78 mmol) in THF (150 mL) was added triethylamine (17.9 mL, 128.42 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.9*M* in THF, 47.56 mL, 42.81 mmol) was added dropwise. DCM (50 mL) was added. The white slurry was stirred at rt for 3.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (428 uL). Anhydrous $MgSO_4$ (5.7 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 5% triethylamine) as the gradient to afford the title compound as a white foam (13.08 g, 78.2% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.2, 1.4 Hz, 2H), 7.64 (tt, J = 7.4, 1.3 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.46 (dd, J = 8.6, 1.3 Hz, 2H), 7.35 (d, J = 8.6 Hz, 4H), 7.29 (t, J = 7.6 Hz, 2H), 7.22 (tt, J = 7.3, 1.3 Hz, 1H), 6.84 (d, J = 8.9 Hz, 4H), 4.99 (q, J = 6.1 Hz, 1H), 4.07 (dt, J = 6.2, 1.9 Hz, 1H), 3.89 (ddd, J = 10.1, 8.1, 5.9 Hz, 1H), 3.82 (td, J = 8.0, 2.8 Hz, 1H), 3.79 (s, 6H), 3.79 – 3.75 (m, 1H), 3.61 (dq, J = 9.7, 5.9 Hz, 1H), 3.47 (dd, J = 14.5, 6.8 Hz, 1H), 3.45 – 3.38 (m, 2H), 3.34 (dd, J = 14.5, 5.6 Hz, 1H), 3.29 (ddd, J = 11.1, 8.7, 4.6 Hz, 1H), 3.00 (qd, J = 10.5, 4.1 Hz, 1H), 1.83 (dtt, J = 11.9, 7.7, 3.3 Hz, 1H), 1.74 (dq, J = 11.9, 7.5 Hz, 1H), 1.61 (qd, J = 7.7, 6.6, 3.0 Hz, 1H), 1.56 (dddd, J = 13.7, 10.0, 5.8, 3.9 Hz, 1H), 1.38 (ddt, J = 13.0, 5.4, 2.1 Hz, 1H), 1.07 (dq, J = 11.5, 9.8 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 152.11; MS (ESI), 704.87 $[M + H]^+$.

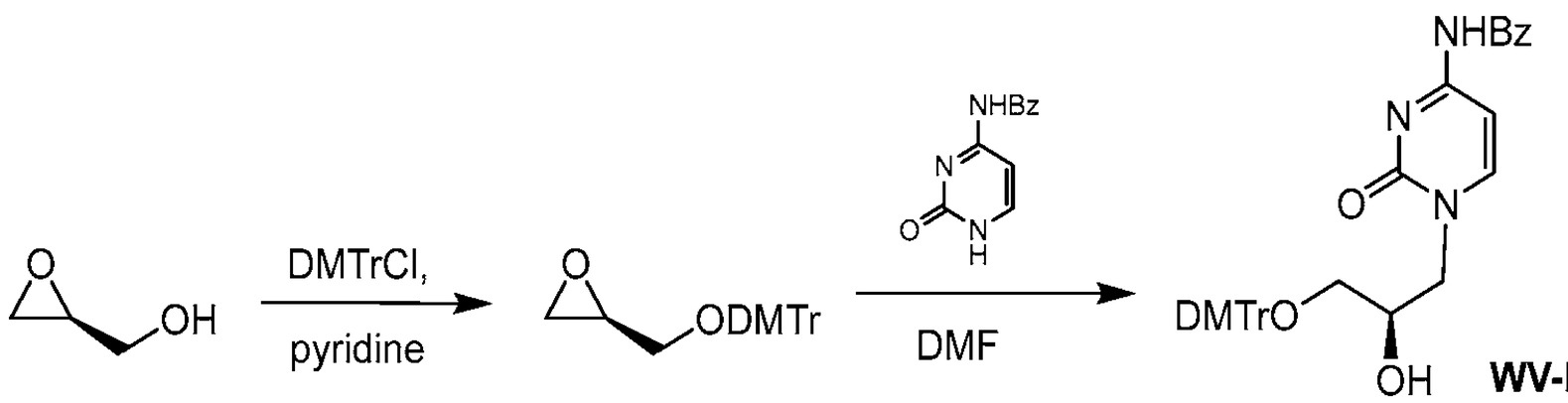
[001212] Synthesis of (S)-N-(1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide (WV-NU-175)



WV-NU-175

[001213] To a solution of (S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (34.30 g, 159.39 mmol, 1 *eq.*) in DMF (300 mL) was added NaH (1.27 g, 31.88 mmol, 60% purity, 0.2 *eq.*) the mixture was stirred at 20 °C for 2 hr, and then (2S)-2-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]oxirane (60 g, 159.39 mmol, 1 *eq.*) was added. The mixture was stirred at 115 °C for 4 hr. TLC (Petroleum ether: Ethyl acetate = 3:1, Rf = 0.05) indicated compound 2 was consumed and one new spot formed. The solution was subsequently cooled to 20 °C and partitioned between saturated brine 1000 mL and EtOAc (200mL*3). The organic phase was separated, washed twice with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1, 5% TEA). WV-NU-175 (14.9 g, 24.45 mmol, 15.34% yield, 97.094% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.90 - 3.03 (m, 2 H) 3.54 - 3.63 (m, 1 H) 3.73 (d, J = 1.50 Hz, 6 H) 4.02 (s, 1 H) 4.20 (br dd, J = 12.82, 3.06 Hz, 1 H) 5.31 (d, J = 5.88 Hz, 1 H) 6.90 (dd, J = 8.88, 1.75 Hz, 4 H) 7.19 - 7.36 (m, 8 H) 7.43 (d, J = 7.38 Hz, 2 H) 7.48 - 7.55 (m, 2 H) 7.61 (d, J = 7.38 Hz, 1 H) 7.96 - 8.05 (m, 2 H) 11.15 (br s, 1 H); LCMS (M-H$^+$): 590.3; purity: 98.72%.

[001214] Synthesis of (R)-N-(1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide (WV-NU-176)



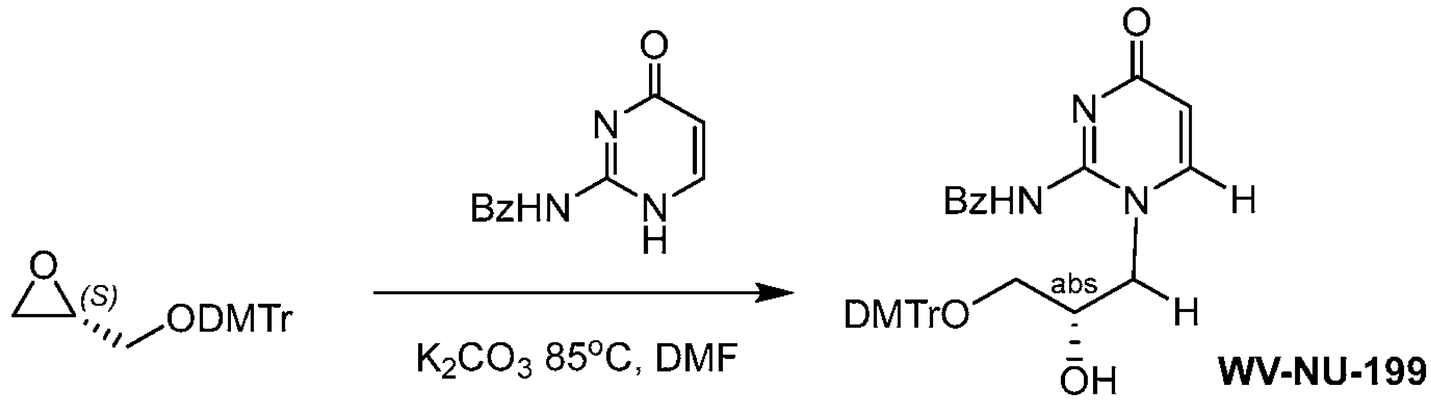
WV-NU-176

[001215] **Step 1**. To a solution of [(2S)-oxiran-2-yl]methanol [(2S)-oxiran-2-yl]methanol (35.7 g, 481.92 mmol, 31.88 mL, 1 eq.) in PYRIDINE (1750 mL) was added DMTCl (179.62 g, 530.11 mmol, 1.1 eq.). The mixture was stirred at 15 °C for 10 hr. TLC (Petroleum ether: Ethyl acetate = 3:1, Rf = 0.70) indicated Reactant 1 was consumed completely and three new spots formed. A few drops of Methanol 30 ml was added to hydrolyze any unreacted DMTrC1 and the mixture was stirred for 10 minutes. The product was washed with H_2O (8000ml), extracted with EAOAC (500 mL * 3). The combined organic layers were washed with NaCl (50mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 3/1， 5%TEA) to give

(R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (240 g, 637.55 mmol, 66.15% yield) as a yellow oil. ^{1}HNMR (400MHz, DMSO-d6) δ = 7.43 - 7.38 (m, 2H), 7.34 - 7.19 (m, 7H), 6.89 (d, J = 8.8 Hz, 4H), 5.31 (d, J = 5.5 Hz, 1H), 3.84 (qd, J = 5.4, 10.4 Hz, 1H), 3.75 - 3.72 (m, 6H), 3.65 - 3.59 (m, 1H), 3.39 - 3.38 (m, 1H), 3.06 - 2.94 (m, 2H).

[001216] **Step 2**. To a solution of (R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (14.29 g, 66.41 mmol, 1 *eq.*) in DMF (250 mL) was added K_2CO_3 (18.36 g, 132.82 mmol, 2 *eq.*). The mixture was stirred at 85°C for 2hr, (2R)-2-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]oxirane (25 g, 66.41 mmol, 1 *eq.*) was added. The mixture was stirred at 85 °C for 12 hr. The mixture was concentrated in vacuo. The residue was quenched by sat. aq. $NaHCO_3$ (500 mL) and then extracted with EtOAc (600 mL * 3). The combined organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was Purified by column chromatograph on silica gel eluted with (Petroleum ether / Ethyl acetate = 50/ 1, 3/ 1) to give WV-NU-176 (24 g, 40.56 mmol, 11.75% yield) as a white solid. ^{1}HNMR (CHLOROFORM-d, 400MHz): δ = 7.94 (s, 2H), 7.83 (br d, J = 7.4 Hz, 2H), 7.50-7.58 (m, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.34 (br d, J = 7.6 Hz, 3H), 7.20-7.29 (m, 7H), 7.12-7.20 (m, 2H), 6.76 (d, J = 8.8 Hz, 4H), 4.28 (dd, J = 13.6, 2.5 Hz, 1H), 4.14 (br s, 1H), 3.74-3.81 (m, 1H), 3.71 (s, 6H), 3.11-3.26 (m, 1H), 3.05 (dd, J = 9.6, 6.0 Hz, 1H), 1.19 ppm (t, J = 7.1 Hz, 2H); LCMS: ($M-H^+$): 590.2, LCMS purity 99.56%.

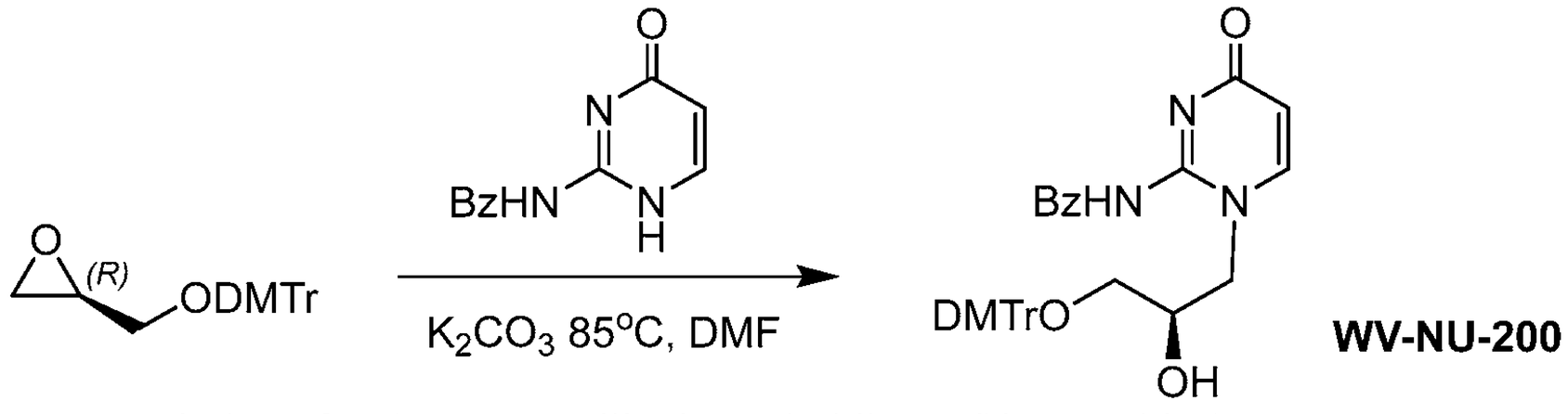
[001217] Synthesis of (S)-N-(1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-4-oxo-1,4-dihydropyrimidin-2-yl)benzamide (WV-NU-199)



[001218] To a solution of compound N-(4-oxo-1,4-dihydropyrimidin-2-yl)benzamide (57.17 g, 265.64 mmol, 2 *eq.*) in DMF (600 mL) was added drop wise K_2CO_3 (9.18 g, 66.41 mmol, 0.5 *eq.*) at 85°C, the mixture was stirred at this temperature for 30 min, and then (S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (50 g, 132.82 mmol, 1 *eq.*) was added drop wise at 85°C. The resulting mixture was stirred at 85°C for 48hr. The reaction mixture was quenched by addition water 150 mL at 15°C, and extracted with Ethyl acetate 1000 mL (500mL *2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1) to give WV-NU-199 (14.23 g, 24.05 mmol, 18.11% yield) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 13.40 - 13.08 (m, 1H), 8.17 (d, J = 7.9 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.53 - 7.42 (m, 3H), 7.33 - 7.20 (m, 9H), 6.85 (d, J = 8.8 Hz, 4H), 5.94 (dd, J = 2.2, 7.9 Hz, 1H), 5.37 (d, J = 5.6 Hz, 1H), 4.67 (dd, J = 3.1, 13.3 Hz, 1H), 4.34 - 4.18 (m, 1H), 3.75 - 3.68 (m, 7H), 3.15 (br dd, J = 4.9, 9.0 Hz, 1H), 2.96 (br t, J = 8.1 Hz, 1H); LCMS (M-H+):592.24, purity: 94.76%.

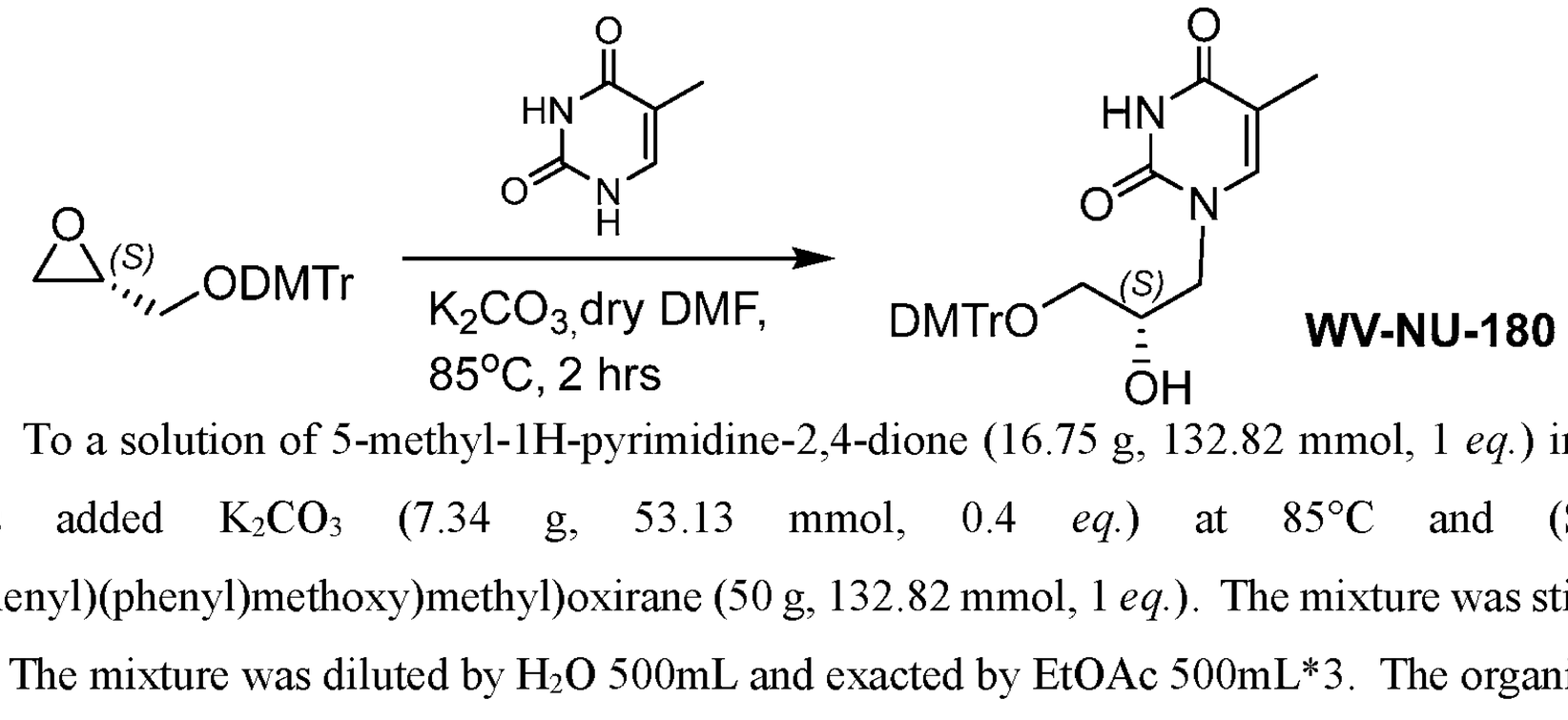
[001219] Synthesis of (R)-N-(1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-4-oxo-

1,4-dihydropyrimidin-2-yl)benzamide (WV-NU-200)



[001220] To a solution of N-(4-oxo-1,4-dihydropyrimidin-2-yl)benzamide (34.30 g, 159.39 mmol, 2 *eq.*) in DMF (350 mL) was added K_2CO_3 (5.51 g, 39.85 mmol, 0.5 *eq.*) at 85°C, the mixture was stirred at this temperature for **30** min, and then (R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (30.00 g, 79.69 mmol, 1 *eq.*) was added drop wise at 85°C. The resulting mixture was stirred at 85°C for 48hr. The reaction mixture was quenched by addition water 50 mL at 15°C, and extracted with Ethyl acetate 200 mL (100mL *2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1) to give WV-NU-200 (7.95 g, 13.44 mmol, 16.86% yield) as a white solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 13.23 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 7.3 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.53 - 7.41 (m, 3H), 7.32 - 7.19 (m, 9H), 6.84 (d, J = 8.9 Hz, 4H), 5.93 (dd, J = 2.4, 8.0 Hz, 1H), 5.36 (d, J = 5.6 Hz, 1H), 4.67 (dd, J = 3.1, 13.3 Hz, 1H), 4.33 - 4.19 (m, 1H), 3.75 - 3.67 (m, 7H), 3.14 (dd, J = 4.9, 9.1 Hz, 1H), 2.96 (br t, J = 8.1 Hz, 1H); LCMS (M-H+):592.24, purity: 93.75%.

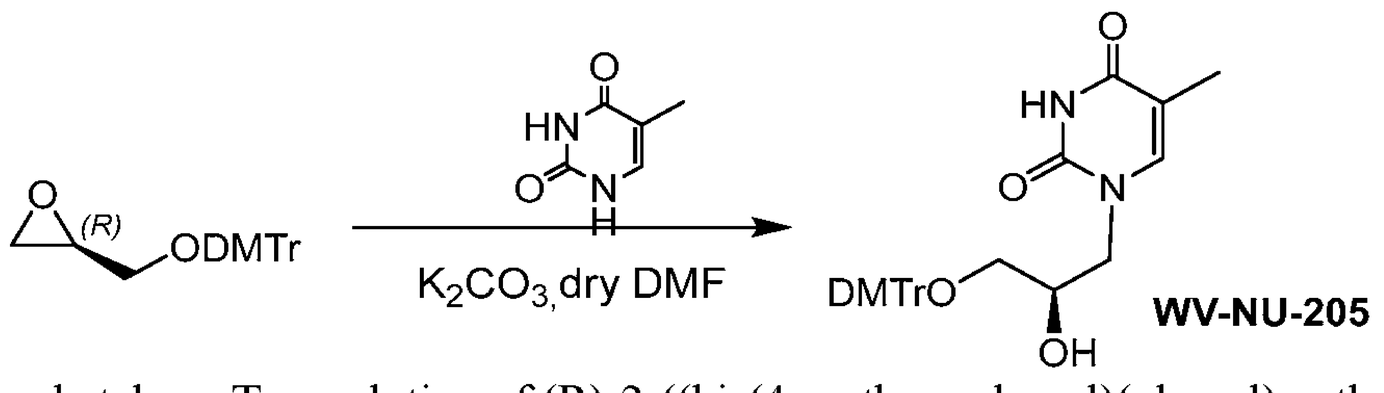
[001221] Synthesis of (S)-1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-5-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-180)



[001222] To a solution of 5-methyl-1H-pyrimidine-2,4-dione (16.75 g, 132.82 mmol, 1 *eq.*) in DMF (100 mL) was added K_2CO_3 (7.34 g, 53.13 mmol, 0.4 *eq.*) at 85°C and (S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (50 g, 132.82 mmol, 1 *eq.*). The mixture was stirred at 85°C for 24 hrs. The mixture was diluted by H_2O 500mL and exacted by EtOAc 500mL*3. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The silica gel column was washed with Petroleum ether (5% Et_3N) 600 mL and Petroleum ether 600mL. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 1/1) to give WV-NU-180 (13.8 g, 26.33 mmol, 19.83% yield, 95.9% purity) as yellow solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 11.20 (s, 1H), 7.50 - 7.13 (m, 10H), 6.88 (dd, J = 1.5, 8.8 Hz, 4H), 5.25 (d, J = 5.6 Hz, 1H), 3.95 - 3.86 (m, 2H), 3.77 - 3.70 (m, 6H), 3.53 - 3.40 (m, 1H), 3.01 - 2.93 (m, 1H), 2.91 - 2.82 (m, 1H), 2.75 - 2.71 (m, 1H), 2.73 (s, 1H), 1.70

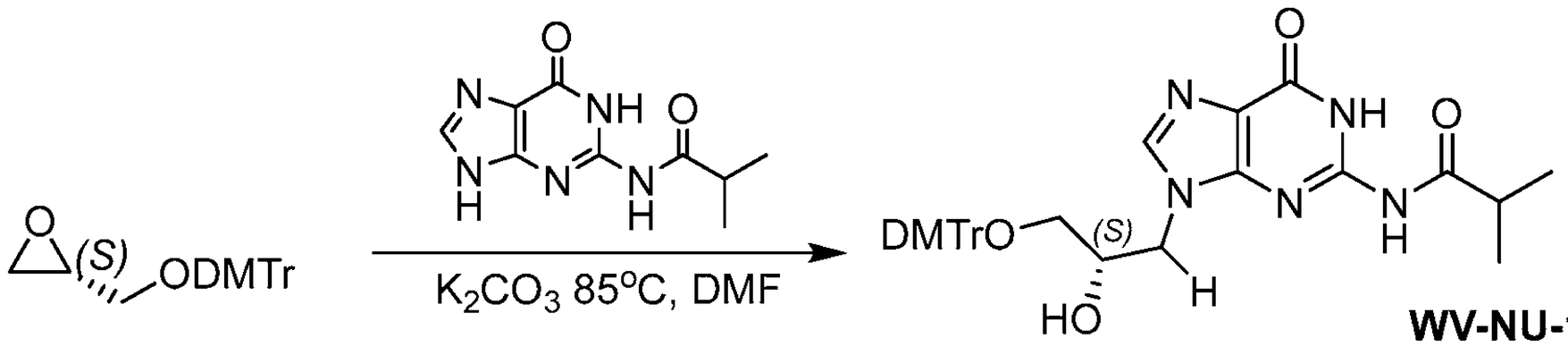
(s, 3H). LCMS: (M^-H^+):501.1, LCMS purity: 95.9%.

[001223] Synthesis of (R)-1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-5-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-205)



[001224] For two batches: To a solution of (R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (60 g, 159.39 mmol, 1 *eq.*) in DMF (600 mL) was added K_2CO_3 (11.01 g, 79.69 mmol, 0.5 *eq.*) at 85 °C for 30 min, and 5-methyl-1H-pyrimidine-2,4-dione (20.10 g, 159.39 mmol, 1 *eq.*) was added. The mixture was stirred at 85 °C for 12 hr. The reaction mixture was quenched by addition water 500 mL at 15°C, and extracted with Ethyl acetate 2000 mL (1000mL *2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Petroleum ether： Ethyl acetate = 1 ： 0 to 0 ： 1) to give WV-NU-205 (10 g, 19.90 mmol) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 11.18 (s, 1H), 7.42 (br d, J = 7.5 Hz, 2H), 7.36 - 7.21 (m, 9H), 6.88 (dd, J = 1.3, 8.7 Hz, 4H), 5.24 (d, J = 5.5 Hz, 1H), 3.95 - 3.86 (m, 2H), 3.74 (s, 6H), 3.46 (br dd, J = 9.4, 14.5 Hz, 1H), 3.01 - 2.85 (m, 2H), 1.70 (s, 3H); LCMS (M-H+):502.56, purity: 96.97%.

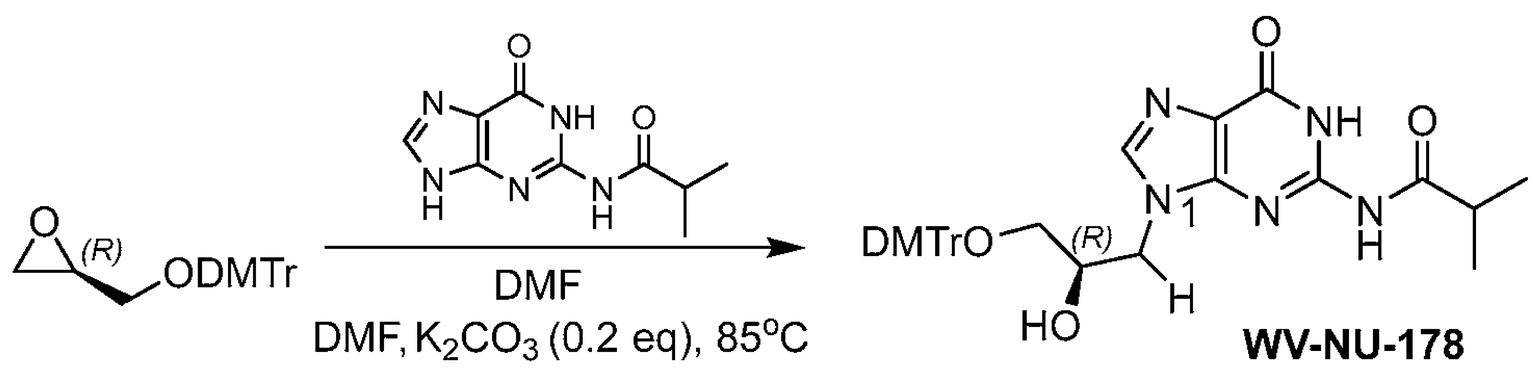
[001225] Synthesis of (S)-N-(9-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (WV-NU-177)



[001226] For three batches: To a solution of 2-methyl-N-(6-oxo-1, 9-dihydropurin-2-yl)propanamide (11.75 g, 53.13 mmol, 1 *eq.*) in DMF (200 mL) was added K_2CO_3 (3.67 g, 26.56 mmol, 0.5 *eq.*) at 85°C for 30 min, and (S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (20 g, 53.13 mmol, 1 *eq)* was added. The mixture was stirred at 85°C for 12 hr. Three reactions were combined for workup. The reaction mixture was diluted with water 500 mL and extracted with EtOAc (500 mL * 4). The combined organic layers were dried over Na_2SO_4 filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane : Methanol = 0:1 to 30： 1). The mixture of 22 g crude was purified by prep-HPLC column (Phenomenex Titank C18 Bulk 250*100mm 10u; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 45%-65%, 20min) to give Compound **WV-NU-177** (8.1 g, 13.55 mmol, 36.82% yield) as a light yellow solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 12.03 (s, 1H), 11.56 (s, 1H), 7.89 - 7.86 (m, 1H), 7.43 - 7.37 (m, 2H), 7.33 - 7.18 (m, 7H), 6.90 - 6.84 (m, 4H), 5.42 (d, J = 5.0 Hz, 1H), 4.15 - 4.08 (m, 2H),

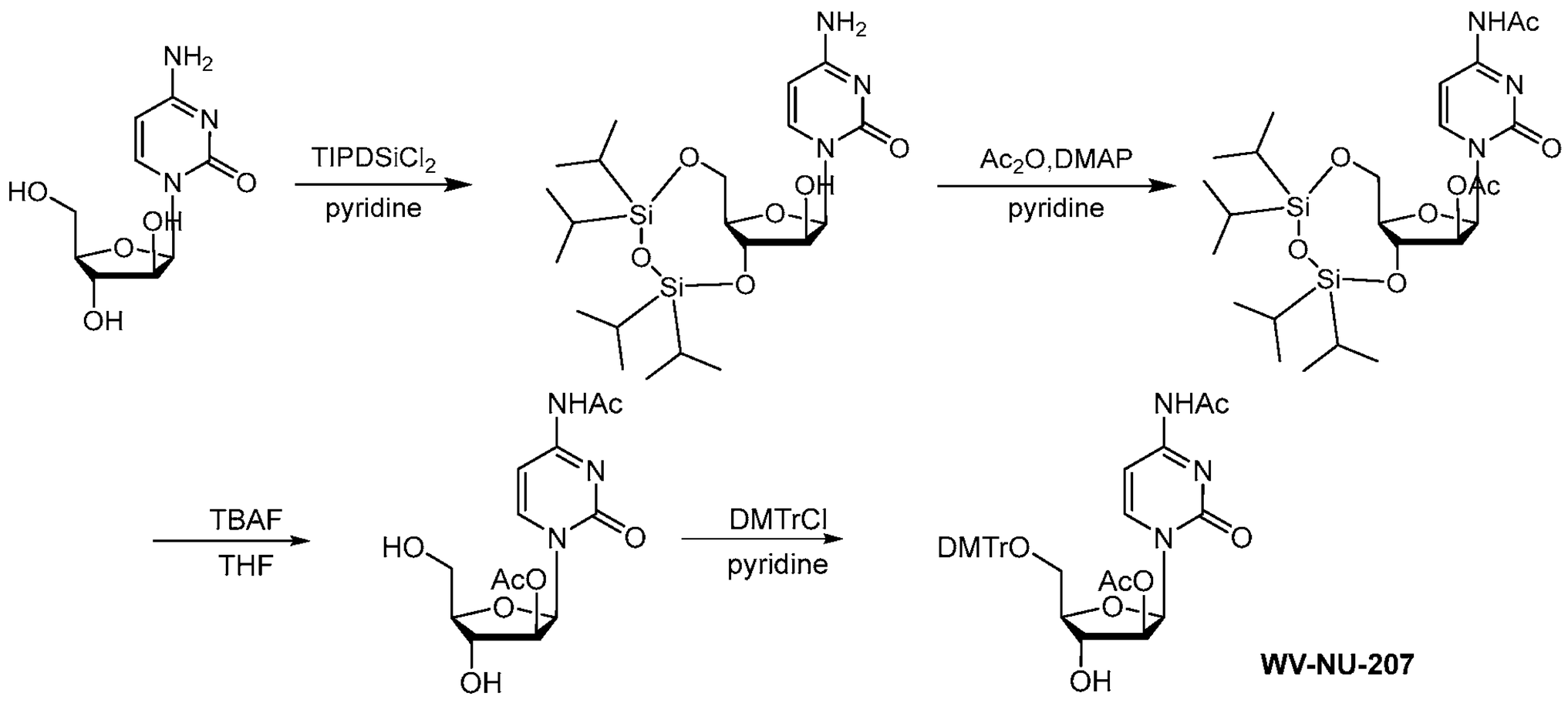
3.73 (d, J = 0.8 Hz, 6H), 3.34 (s, 1H), 3.01 - 2.96 (m, 1H), 2.89 (dd, J = 4.1, 9.4 Hz, 1H), 2.78 (quin, J = 6.8 Hz, 1H), 1.11 (dd, J = 2.6, 6.9 Hz, 6H); LCMS (M-H+):597.26, LCMS purity: 97.82%.

[001227] Synthesis of ((R)-N-(9-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (WV-NU-178)



[001228] For 5 batches: To a solution of (R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane (14 g, 37.19 mmol, 1 eq) in DMF (100 mL) was added K_2CO_3 (2.06 g, 14.88 mmol, 0.4 eq.) and 2-methyl-N-(6-oxo-1,9-dihydropurin-2-yl) propanamide (8.23 g, 37.19 mmol, 1 eq.). The mixture was stirred at 85 °C for 12 hrs. The reaction mixture was quenched by addition water 500 mL at 15°C, and extracted with Ethyl acetate 1000 mL (500mL *2). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by pre-HPLC （column: Phenomenex Titank C18 Bulk 250*100mm 10u; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 50%-70%,20min) to give compound WV-NU-178 (8 g, 13.39 mmol, 32.01% yield) as a white solid. ^{1}HNMR (CHLOROFORM-d, 400MHz): δ = 7.59 (s, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.30-7.36 (m, 6H), 7.22-7.27 (m, 1H), 6.85 (d, J = 8.8 Hz, 4H), 4.26 (br d, J = 11.3 Hz, 2H), 4.10 (br dd, J = 14.8, 8.3 Hz, 2H), 3.82 (s, 6H), 3.16-3.29 (m, 2H), 2.57-2.65 (m, 1H), 1.30 ppm (dd, J = 6.8, 4.8 Hz, 6H). LCMS: M-H$^+$: 596.6, LCMS purity 99.48%.

[001229] Synthesis of (2R,3S,4R,5R)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl acetate (WV-NU-207)



[001230] Step 1. To a solution of 4-amino-1-((2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (96 g, 394.71 mmol, 1 *eq.*) in pyridine (460 mL) at 0°C drops added chloro-[chloro(diisopropyl)silyl]oxy-diisopropyl-silane (136.95 g, 434.18 mmol, 138.90

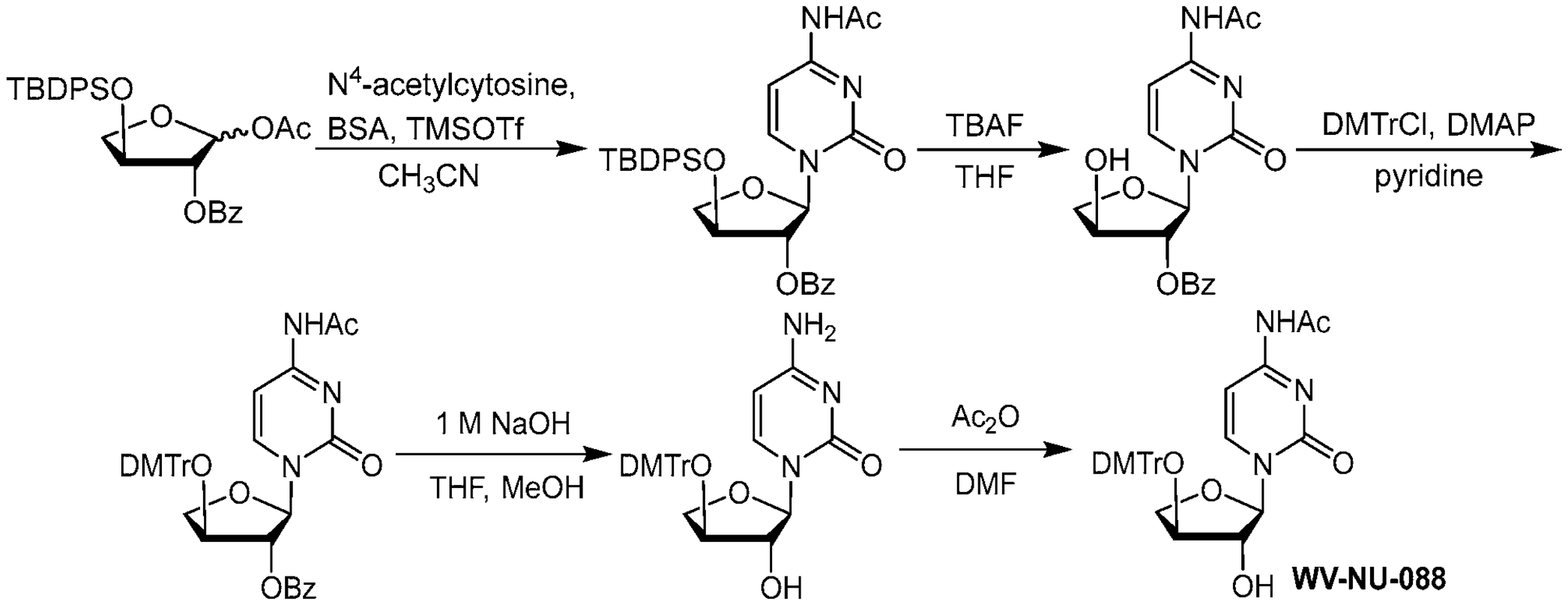
mL, 1.1 *eq.*) in N_2. And 2 hr, the mixture was stirred at 0-20°C for 10 hr. The reaction mixture was vacuum concentrated to obtain crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=10:1 to 0:1) to give 4-amino-1-((6aR,8R,9S,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidin-2(1H)-one (170 g, 350.00 mmol, 88.67% yield) was obtained as a white solid. LCMS ($M+H^+$): 486.3.

[001231] Step 2. To a solution of 4-amino-1-((6aR,8R,9S,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidin-2(1H)-one (170 g, 350.00 mmol, 1 *eq.*) in PYRIDINE (1700 mL) was added DMAP (85.52 g, 699.99 mmol, 2 *eq.*) and Ac_2O (142.92 g, 1.40 mol, 131.12 mL, 4 *eq.*). The mixture was stirred at 25 °C for 10 hr. The reaction mixture was diluted with water 1000 mL, and then separate and collect organic phases. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (6aR,8R,9S,9aR)-8-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl acetate (199 g, crude) as a yellow oil. LCMS ($M+H^+$):570.4.

[001232] Step 3. For three batches: To a solution of (6aR,8R,9S,9aR)-8-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl acetate (66.3 g, 116.36 mmol, 1 eq.) in THF (600 mL) was added TBAF (1 M, 174.54 mL, 1.5 eq.) and AcOH (6.99 g, 116.36 mmol, 6.66 mL, 1 eq.). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate: MeOH = 20:1 to1:1). After concentration under reduced pressure, 1 L ethyl acetate was stirred for 10 min, filtered to obtain (2R,3S,4R,5R)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl acetate (64 g, 195.55 mmol, 64.00% yield) was obtained as a white solid. ^{1}HNMR (400 MHz, DMSO-d6) δ = 10.89 (br s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.17 (d, J = 4.8 Hz, 1H), 5.85 (br d, J = 4.1 Hz, 1H), 5.26 (t, J = 4.3 Hz, 1H), 5.12 (br s, 1H), 4.09 (br s, 2H), 3.87 (q, J = 4.8 Hz, 1H), 3.63 - 3.57 (m, 1H), 3.16 (d, J = 4.4 Hz, 2H), 2.10 (s, 3H), 1.85 (s, 3H); LCMS ($M+H^+$): 328.2; purity: 73.59%.

[001233] Step 4. For two batches: To a solution of (2R,3S,4R,5R)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl acetate (26 g, 79.44 mmol, 1 eq.) in pyridine (500 mL) was added DMTCl (26.92 g, 79.44 mmol, 1 eq.). The mixture was stirred at 25 °C for 20 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2, Ethyl acetate: MeOH = 20:1 to 1:1, 5%TEA) to give WV-NU-207 (46.5 g, 73.85 mmol, 46.50% yield) as a yellow solid. ^{1}HNMR (400 MHz, DMSO-d6) δ = 10.90 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.43 - 7.39 (m, 2H), 7.36 - 7.22 (m, 8H), 7.11 (d, J = 7.5 Hz, 1H), 6.91 (dd, J = 1.3, 8.8 Hz, 4H), 6.20 (d, J = 4.8 Hz, 1H), 5.94 (d, J = 4.6 Hz, 1H), 5.26 - 5.22 (m, 1H), 4.17 - 4.09 (m, 2H), 3.74 (s, 6H), 3.32 - 3.28 (m, 2H), 2.10 (s, 3H), 1.74 (s, 3H); LCMS ($M-H^+$):628.2; purity: 96.49%.

[001234] Synthesis of N-(1-((2R,3R,4S)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)-3-hydroxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (WV-NU-088)



[001235] **Step 1.** To a solution of (3R,4S)-2-acetoxy-4-((tert-butyldiphenylsilyl)oxy)tetrahydrofuran-3-yl benzoate (27.5 g, 54.49 mmol, 1 *eq.*) and N-(2-oxo-1H-pyrimidin-4-yl)acetamide (8.76 g, 57.22 mmol, 1.05 *eq.*) in MeCN (140 mL) was added BSA (23.28 g, 114.44 mmol, 28.29 mL, 2.1 *eq.*), and the mixture was stirred for 30 min at 60 °C. TMSOTf (19.38 g, 87.19 mmol, 15.76 mL, 1.6 *eq.*) was added dropwise, and stirring was continued for another 2 h at 60 °C. The mixture was cooled to r.t, diluted with 100 mL of EtOAc, and poured into 200 mL of cold sat. aq. $NaHCO_3$ solution with stirring, and the mixture was extracted with DCM (500 mL*2). The organic layer was separated and washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to get (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)tetrahydrofuran-3-yl benzoate (30 g, crude) as a yellow solid. The mixture was used directly without further purification. LCMS: ($M+H^+$): 598.3.

[001236] **Step 2.** To a solution of (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)tetrahydrofuran-3-yl benzoate (30 g, 50.19 mmol, 1 *eq.*) in THF (240 mL) was added TBAF (1 M, 75.28 mL, 1.5 *eq.*). The mixture was stirred at 0 °C for 1 hr. TLC (Ethyl acetate / Petroleum ether = 2:1, R_f = 0.25) showed one main spot. The solvent was evaporated under reduced pressure, and the residue was dissolved in 600 mL of EtOAc. The organic layer was separated and washed with H_2O (100 mL*2) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a crude. The residue was purified by column chromatography (SiO_2, Petroleum ether / Ethyl acetate = 5/1 to 1/2) to get (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-hydroxytetrahydrofuran-3-yl benzoate (12 g, 33.40 mmol, 66.54% yield) as a yellow solid.

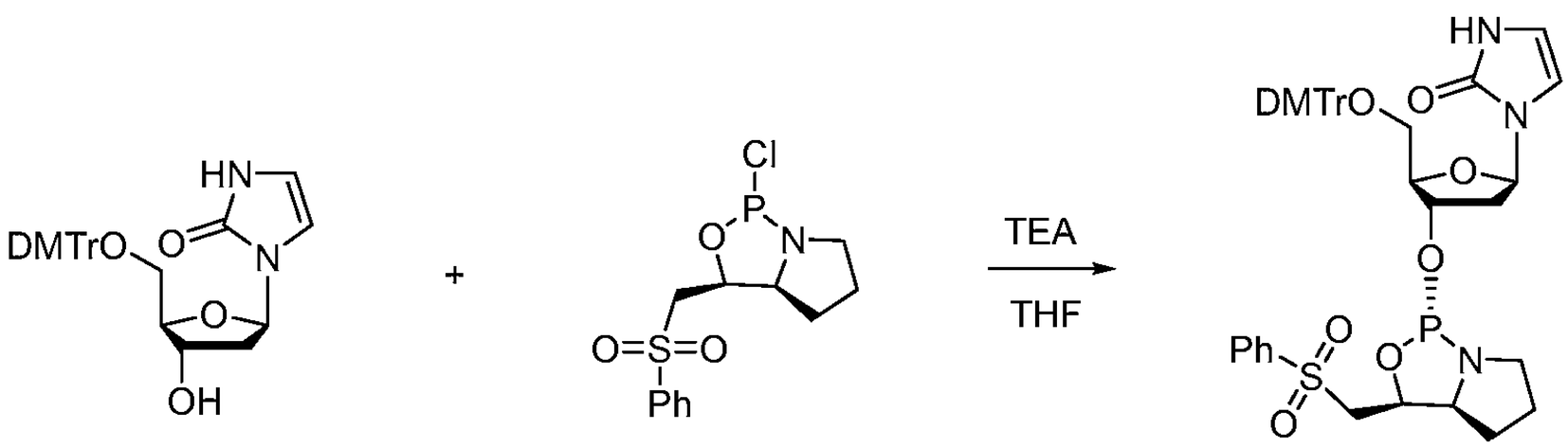
[001237] **Step 3**: A mixture of (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-hydroxytetrahydrofuran-3-yl benzoate (11 g, 30.61 mmol, 1 *eq.*), DMTCl (15.56 g, 45.92 mmol, 1.5 *eq.*), DMAP (373.98 mg, 3.06 mmol, 0.1 *eq.*) was co-evaporated twice with 20 mL of anhydrous pyridine. The mixture was dissolved in anhydrous pyridine (80 mL) and stirred under argon at 80 °C for 16 h. The mixture was concentrated to get the crude. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 10/1, 3/1, 5%TEA) to get (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)tetrahydrofuran-3-yl benzoate (18.5 g, crude) as white solid. LCMS:

($M\text{-}H^+$): 660.2.

[001238] Step 4. To a solution of (2R,3R,4S)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)tetrahydrofuran-3-yl benzoate (18.5 g, 27.96 mmol, 1 *eq.*) in the mixture of MeOH (180 mL), $LiOH.H_2O$ (1.41 g, 33.55 mmol, 1.2 *eq.*) was added at 0 °C. Water (500 mL) was added, and then concentrated under reduced pressure to remove the organic solvent. The water phase was extracted with EtOAc (250 mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-amino-1-((2R,3R,4S)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)-3-hydroxytetrahydrofuran-2-yl)pyrimidin-2(1H)-one (14.4 g, crude) as a yellow solid.

[001239] Step 5. To a solution of 4-amino-1-((2R,3R,4S)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)-3-hydroxytetrahydrofuran-2-yl)pyrimidin-2(1H)-one (14.4 g, 27.93 mmol, 1 *eq.*) in DMF (100 mL) was added Ac_2O (3.14 g, 30.72 mmol, 2.88 mL, 1.1 *eq.*), the mixture was stirred at 20 °C for 12 hr. Water (500 mL) was added and extracted with EtOAc (500 mL*2) and the organic was dried over Na_2SO_4, filtered and concentrated to get the crude. The mixture was purified by silica gel chromatography (DCM / Ethyl acetate = 20/1, 1/1, Ethyl acetate : Methanol = 20: 1, 5% TEA) to get the compound WV-NU-088 (8.3 g, 14.45 mmol, 51.73% yield, 97.07% purity) as a white solid. ^{1}HNMR (400MHz, CHLOROFORM-d) δ = 9.23 (br s, 1H), 8.04 (d, J=7.5 Hz, 1H), 7.54 (d, J=7.4 Hz, 1H), 7.38 - 7.33 (m, 2H), 7.31 - 7.18 (m, 8H), 6.86 - 6.78 (m, 4H), 4.34 - 4.24 (m, 3H), 3.80 (d, J=2.4 Hz, 6H), 3.69 (dd, J=4.4, 9.9 Hz, 1H), 3.39 (dd, J=2.3, 9.8 Hz, 1H), 2.34 (s, 3H), 2.00 (s, 1H) ; LCMS purity: 97.07%, 556.2 $(M\text{-}H)^-$.

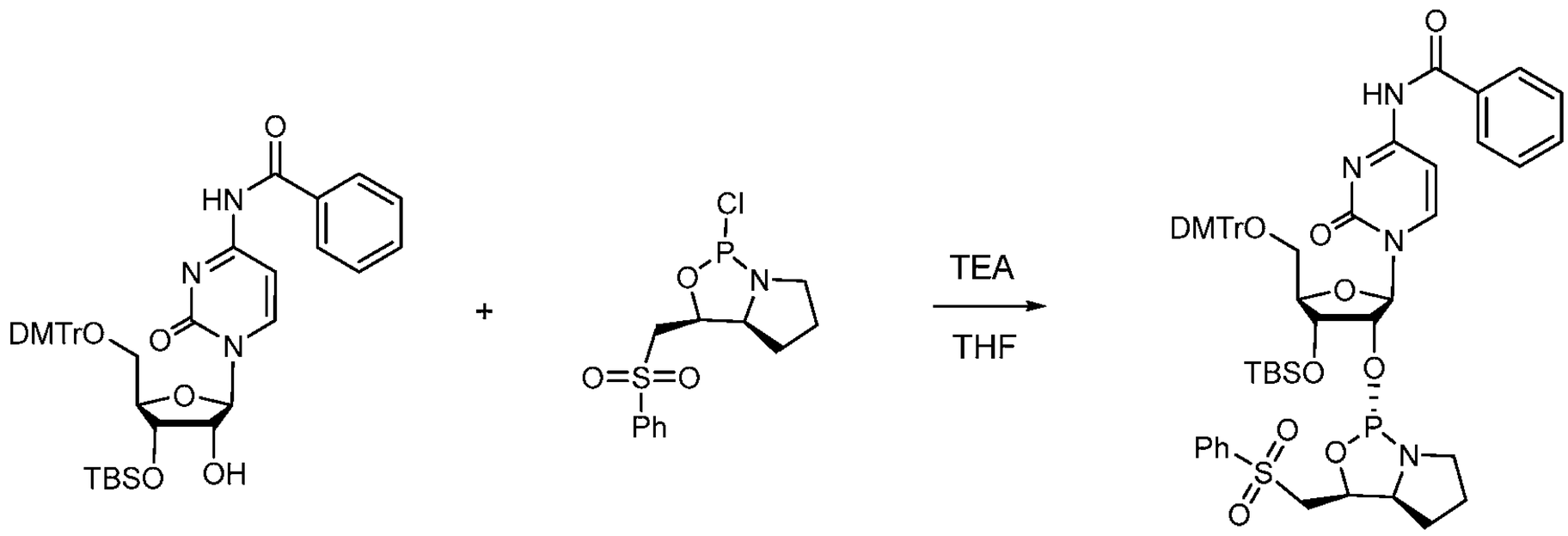
[001240] Synthesis of 1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-1,3-dihydro-2H-imidazol-2-one



[001241] To a solution of dry 3-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-1H-imidazol-2-one (4.0 g, 7.96 mmol) in THF (40 mL) was added triethylamine (4.99 mL, 35.82 mmol). Cooled to 0°C. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.90*M* in THF, 13.27 mL, 11.94 mmol) was added dropwise. The resulting slurry was stirred at 0°C for 2.5 hr then at rt for 1.5 hr. The reaction was quenched by water (72 μL). Anhydrous $MgSO_4$ (960 mg) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 0-100% MeCN in EtOAc (each mobile phase contained 2.5% triethylamine) as the gradient to afford the title compound as a white foam (2.389 g, 38.2% yield). ^{1}H NMR

(600 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.90 – 7.86 (m, 2H), 7.62 – 7.56 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.31 (dd, *J* = 8.7, 5.5 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 4H), 6.34 (t, *J* = 2.6 Hz, 1H), 6.21 (t, *J* = 2.7 Hz, 1H), 6.07 (t, *J* = 7.0 Hz, 1H), 4.92 (q, *J* = 6.1 Hz, 1H), 4.75 (dq, *J* = 8.8, 3.8, 3.4 Hz, 1H), 3.96 (q, *J* = 3.4 Hz, 1H), 3.78 (s, 6H), 3.58 (dq, *J* = 11.8, 6.0 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.35 (dd, *J* = 14.6, 5.3 Hz, 1H), 3.31 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.18 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.09 (qd, *J* = 10.1, 3.9 Hz, 1H), 2.31 (dd, *J* = 7.0, 4.4 Hz, 2H), 1.87 (dh, *J* = 12.6, 4.7, 3.7 Hz, 1H), 1.81 – 1.71 (m, 1H), 1.65 – 1.62 (m, 1H), 1.15 – 1.05 (m, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 152.36; MS (ESI) , 784.77 $[M - H]^-$.

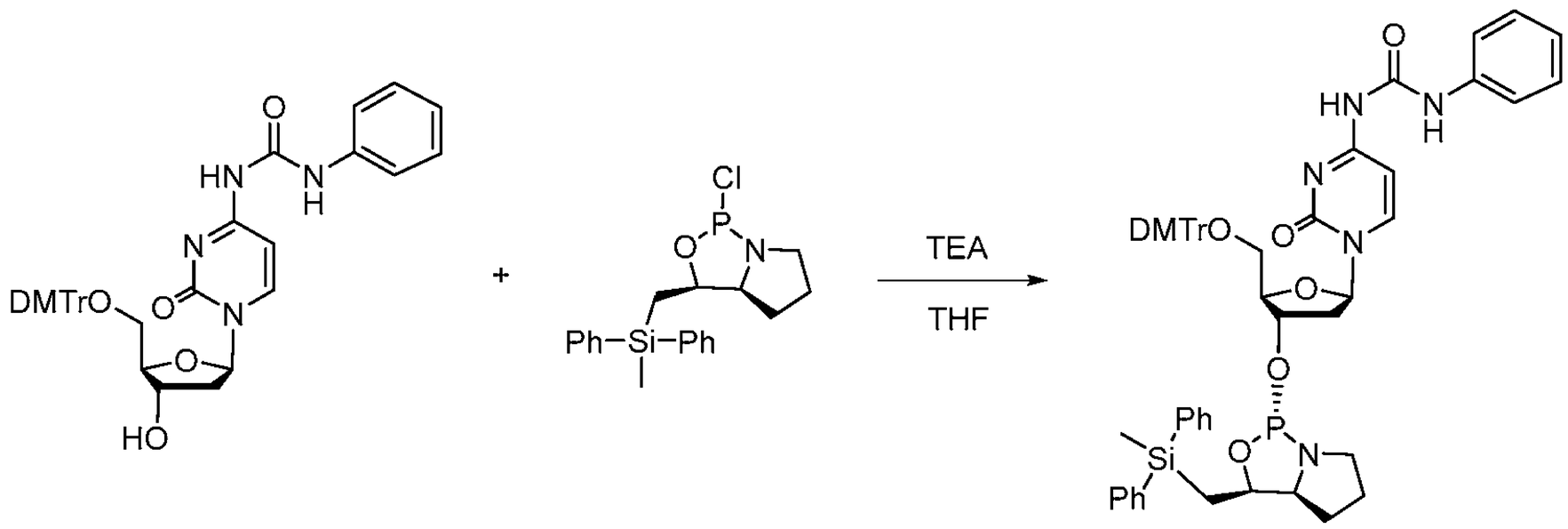
[001242] Synthesis of N-(1-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-3-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide



[001243] To a solution of dry N-[1-[(2R,3S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[tert-butyl(dimethyl)silyl]oxy-3-hydroxy-tetrahydrofuran-2-yl]-2-oxo-pyrimidin-4-yl]benzamide (10.0 g, 13.09 mmol) in THF (100 mL) was added triethylamine (9.85 mL, 70.69 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.90*M* in THF, 26.18 mL, 23.56 mmol) was added dropwise. The resulting slurry was stirred at rt for 2.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (234 μL). Anhydrous $MgSO_4$ (3.12 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-70% EtOAc in hexane (each mobile phase contained 5% triethylamine) as the gradient to afford the title compound as an off-white foam (9.95 g, 72.6% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 8.57 (bs, 2H), 7.99 – 7.95 (m, 2H), 7.91 – 7.82 (m, 2H), 7.64 – 7.58 (m, 2H), 7.52 (dt, *J* = 15.0, 7.6 Hz, 4H), 7.41 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 8.8, 3.2 Hz, 5H), 6.88 (d, *J* = 8.5 Hz, 4H), 5.93 (d, *J* = 1.6 Hz, 1H), 5.14 (q, *J* = 6.3 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.20 (dd, *J* = 8.0, 4.3 Hz, 1H), 4.15 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.83 (s, 6H), 3.79 – 3.69 (m, 3H), 3.59 – 3.54 (m, 1H), 3.51 (dd, *J* = 14.7, 6.9 Hz, 1H), 3.43 – 3.39 (m, 1H), 3.35 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.20 (qd, *J* = 9.4, 4.1 Hz, 1H), 1.82 (tt, *J* = 8.3, 4.3 Hz, 1H), 1.79 – 1.74 (m, 1H), 1.65 (ddt, *J* = 12.2, 6.1, 3.0 Hz, 1H), 1.18 – 1.11 (m, 1H), 0.75 (s, 9H), -0.03 (s, 3H), -0.12 (s, 3H);

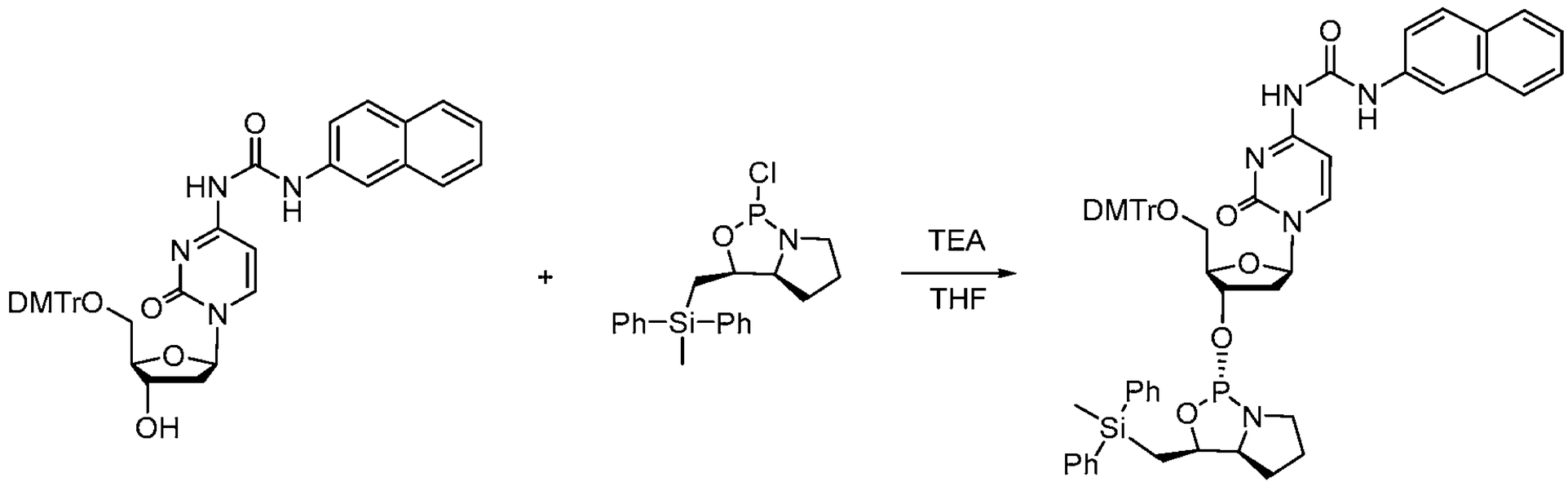
^{31}P NMR (243 MHz, $CDCl_3$) δ 155.49; MS (ESI) , 1045.67 $[M - H]^-$.

[001244] Synthesis of 1-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylurea



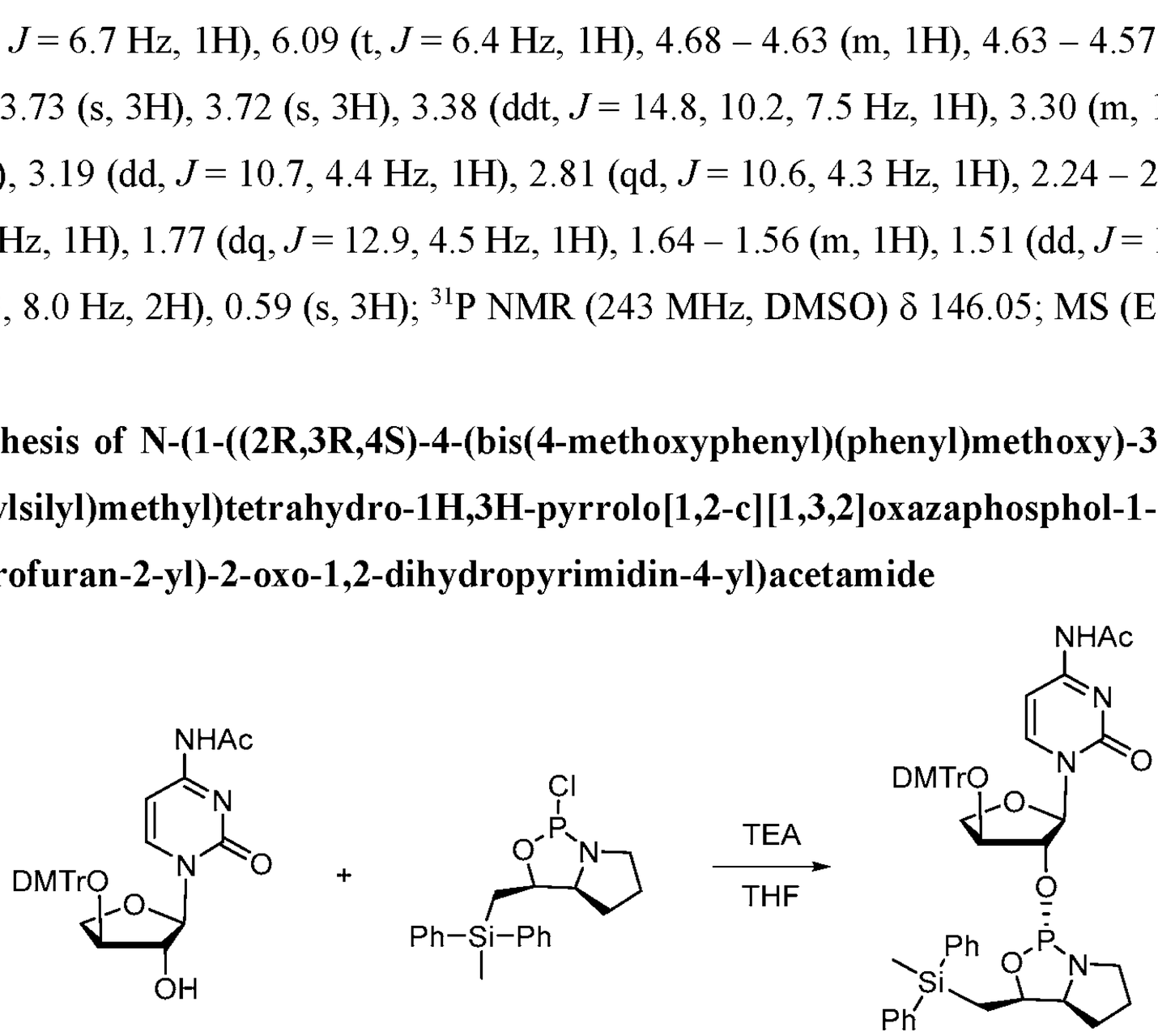
[001245] To a solution of dry 1-[1-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-2-oxo-pyrimidin-4-yl]-3-phenyl-urea (10.0 g, 15.42 mmol) in THF (100 mL) was added triethylamine (11.6 mL, 83.24 mmol). [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 28.98 mL, 27.75 mmol) was added dropwise. The resulting off-white slurry was stirred at rt for 3.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (277 μL). Anhydrous $MgSO_4$ (3.7 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexane (each mobile phase contained 2.5% triethylamine) as the gradient to afford the title compound as an off-white foam (9.18 g, 60.3% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.38 (s, 1H), 11.05 (s, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 4H), 7.36 (t, *J* = 8.6 Hz, 3H), 7.30 (m, 9H), 7.26 – 7.21 (m, 6H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 4H), 6.28 (t, *J* = 6.3 Hz, 1H), 4.78 – 4.68 (m, 2H), 3.93 (q, *J* = 3.3 Hz, 1H), 3.77 (s, 6H), 3.52 (ddt, *J* = 15.1, 10.5, 7.6 Hz, 1H), 3.32 (qd, *J* = 10.6, 2.9 Hz, 3H), 3.08 (dt, *J* = 10.8, 6.8 Hz, 1H), 2.60 (ddd, *J* = 14.1, 6.3, 4.0 Hz, 1H), 2.05 (m, 1H), 1.84 (dh, *J* = 12.7, 4.7, 3.9 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.56 – 1.52 (m, 1H), 1.40 (dq, *J* = 15.8, 7.2, 6.7 Hz, 2H), 1.23 – 1.18 (m, 1H), 0.58 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 153.22; MS (ESI) , 986.91 $[M - H]^-$.

[001246] Synthesis of 1-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(naphthalen-2-yl)urea



[001247] To a solution of dry 1-[1-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-2-oxo-pyrimidin-4-yl]-3-(2-naphthyl)urea (15.0 g, 21.47 mmol) in THF (150 mL) was added triethylamine (16.16 mL, 115.92 mmol). [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 40.36 mL, 38.64 mmol) was added dropwise. The resulting off-white slurry was stirred at rt for 3.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (386 μL). Anhydrous $MgSO_4$ (5.15 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 10-60% EtOAc in hexane (each mobile phase contained 5% triethylamine) as the gradient to afford the title compound as an off-white foam (15.91 g, 71.4% yield). ^{1}H NMR (600 MHz, DMSO) δ 12.56 (s, 1H), 10.56 (s, 1H), 8.48 – 8.43 (m, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.54 – 7.45 (m, 5H), 7.39 – 7.27 (m, 8H), 7.27 – 7.20 (m, 8H), 6.88 (dd, *J* = 8.5, 5.7 Hz, 4H), 6.17 (d, *J* = 6.7 Hz, 1H), 6.09 (t, *J* = 6.4 Hz, 1H), 4.68 – 4.63 (m, 1H), 4.63 – 4.57 (m, 1H), 3.84 (q, *J* = 4.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.38 (ddt, *J* = 14.8, 10.2, 7.5 Hz, 1H), 3.30 (m, 1H), 3.23 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.19 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.81 (qd, *J* = 10.6, 4.3 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.88 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.77 (dq, *J* = 12.9, 4.5 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.51 (dd, *J* = 14.8, 5.3 Hz, 1H), 1.45 (dt, *J* = 11.3, 8.0 Hz, 2H), 0.59 (s, 3H); ^{31}P NMR (243 MHz, DMSO) δ 146.05; MS (ESI), 1036.85 $[M-H]^-$.

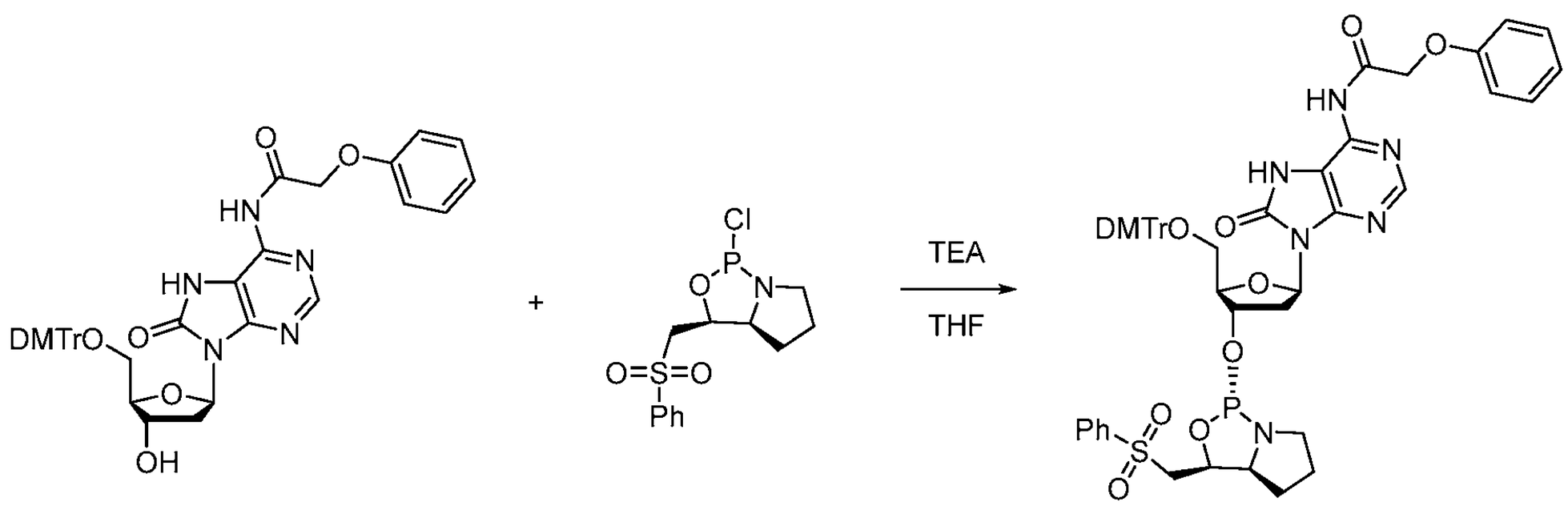
[001248] Synthesis of N-(1-((2R,3R,4S)-4-(bis(4-methoxyphenyl)(phenyl)methoxy)-3-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide



[001249] To a solution of dry N-[1-[(2R,4R)-4-[bis(4-methoxyphenyl)-phenyl-methoxy]-3-hydroxy-

tetrahydrofuran-2-yl]-2-oxo-pyrimidin-4-yl]acetamide (4.0 g, 7.17 mmol) in THF (40 mL) was added triethylamine (5.4 mL, 38.74 mmol). [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 13.49 mL, 12.91 mmol) was added dropwise. The reaction slurry was stirred at rt for 3 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (129 μL). Anhydrous $MgSO_4$ (1.72 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-70% EtOAc in hexane (each mobile phase contained 2.5% triethylamine) as the gradient to afford the title compound as a white foam (4.4 g, 68.4% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.45 (m, 4H), 7.43 – 7.37 (m, 3H), 7.35 (q, *J* = 6.8 Hz, 3H), 7.32 – 7.28 (m, 3H), 7.26 (d, *J* = 4.3 Hz, 3H), 7.21 (p, *J* = 4.2 Hz, 1H), 7.18 (dd, *J* = 8.7, 4.3 Hz, 4H), 6.80 (t, *J* = 8.7 Hz, 4H), 5.65 (s, 1H), 4.76 (q, *J* = 6.8 Hz, 1H), 4.39 (d, *J* = 8.2 Hz, 1H), 4.09 (d, *J* = 3.6 Hz, 1H), 3.79 – 3.75 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.61 (ddt, *J* = 14.9, 10.4, 7.6 Hz, 1H), 3.42 (d, *J* = 9.9 Hz, 1H), 3.36 (ddd, *J* = 13.3, 10.2, 5.8 Hz, 1H), 3.21 (dt, *J* = 11.0, 6.9 Hz, 1H), 2.29 (s, 3H), 1.83 (dp, *J* = 12.7, 4.7 Hz, 1H), 1.69 – 1.61 (m, 1H), 1.53 (dd, *J* = 14.6, 7.9 Hz, 1H), 1.41 (dd, *J* = 14.6, 7.0 Hz, 1H), 1.38 – 1.32 (m, 1H), 1.21 (p, *J* = 10.2 Hz, 1H), 0.53 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 158.33; MS (ESI), 895.65 $[M-H]^-$.

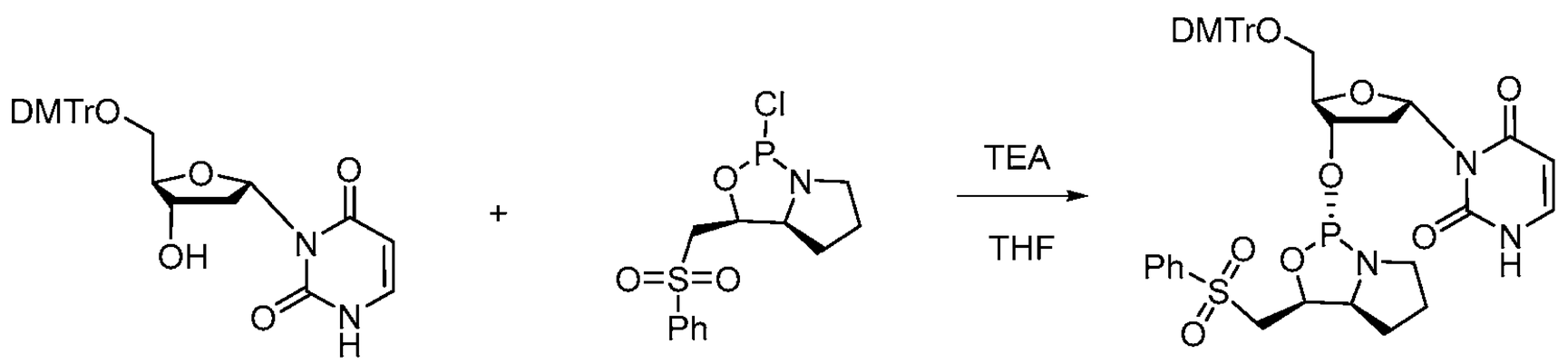
[001250] Synthesis of N-(9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)-2-phenoxyacetamide



[001251] To a solution of dry N-[9-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-8-oxo-7H-purin-6-yl]-2-phenoxy-acetamide (7.5 g, 10.66 mmol) in THF (37.5 mL) was added triethylamine (3.71 mL, 26.64 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.90*M* in THF, 21.31 mL, 19.18 mmol) was added dropwise. The water bath was removed. The off-white slurry was stirred at rt for 3 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (153 μL). Anhydrous $MgSO_4$ (2.04 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 30-100% EtOAc in hexane (each mobile phase contained 1% triethylamine)

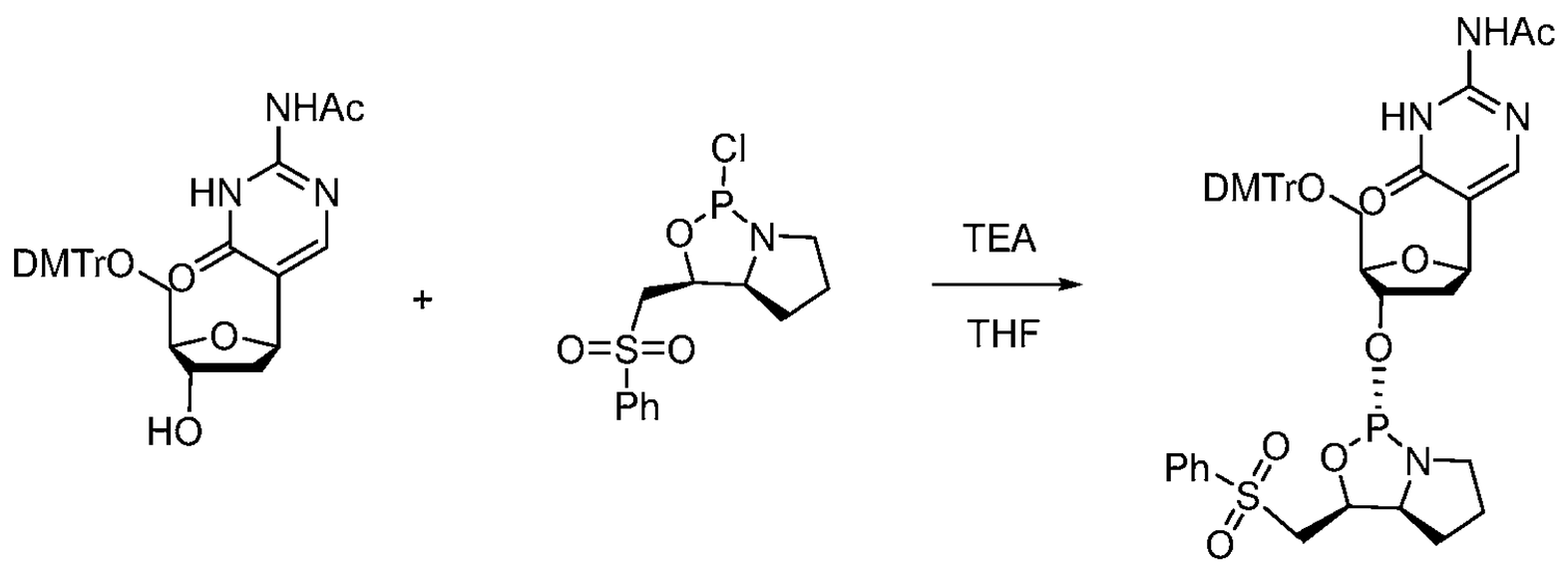
as the gradient to afford the title compound as a white foam (8.35 g, 79.4% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.95 (s, 1H), 8.24 (d, *J* = 1.5 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 4H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.75 (dd, *J* = 8.8, 7.0 Hz, 4H), 6.38 (t, *J* = 6.8 Hz, 1H), 5.09 (h, *J* = 6.2, 5.4 Hz, 2H), 4.67 (s, 2H), 4.06 (q, *J* = 5.1 Hz, 1H), 3.763 (s, 3H), 3.756 (s, 3H), 3.69 (dq, *J* = 11.7, 6.1 Hz, 1H), 3.47 (dt, *J* = 14.7, 8.1 Hz, 2H), 3.37 (dd, *J* = 10.1, 5.1 Hz, 2H), 3.28 (ddd, *J* = 23.8, 11.7, 6.1 Hz, 2H), 3.03 (tt, *J* = 9.8, 5.1 Hz, 1H), 2.30 (dq, *J* = 12.6, 6.3, 5.3 Hz, 1H), 1.88 (ddt, *J* = 13.0, 9.3, 5.1 Hz, 1H), 1.77 (q, *J* = 10.8, 10.0 Hz, 1H), 1.66 (dt, *J* = 12.7, 6.4 Hz, 1H), 1.12 (p, *J* = 10.0 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 149.94; MS (ESI), 985.68 $[M - H]^-$.

[001252] Synthesis of 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione



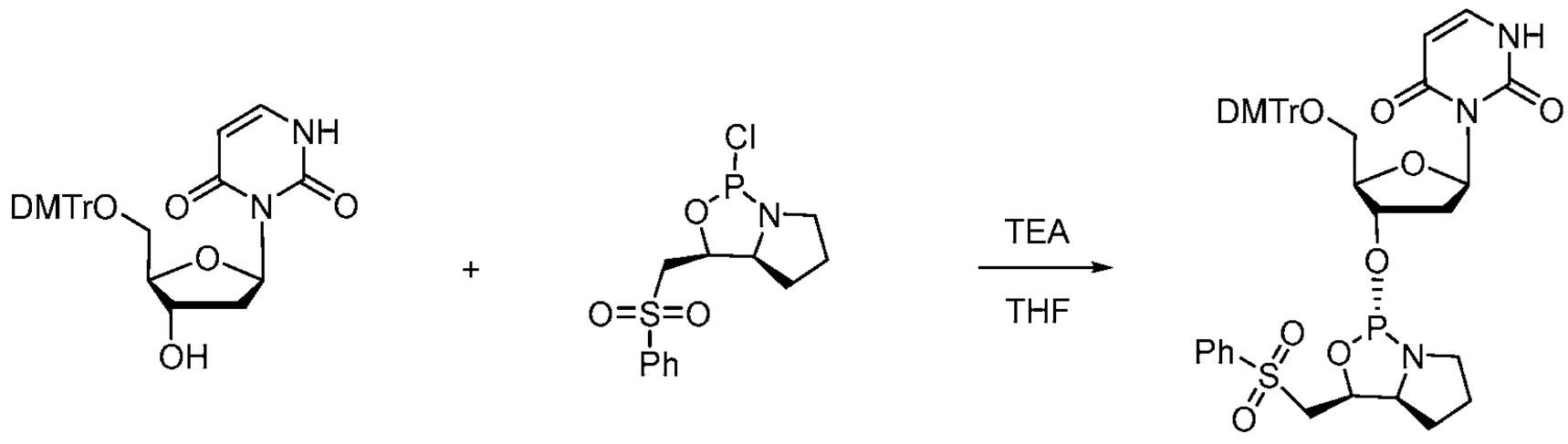
[001253] To a solution of dry 3-[(2S,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-1H-pyrimidine-2,4-dione (3.0 g, 5.65 mmol) in THF (22.5 mL) was added triethylamine (1.97 mL, 14.14 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole) (0.90*M* in THF, 11.31 mL, 10.18 mmol) was added dropwise. The cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (81 μL). Anhydrous $MgSO_4$ (1.08 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 50-100% EtOAc in hexane (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (3.48 g, 75.6% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.90 – 7.85 (m, 2H), 7.62 – 7.57 (m, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 2H), 7.37 – 7.32 (m, 4H), 7.29 – 7.24 (m, 2H), 7.21 – 7.16 (m, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.86 – 6.78 (m, 4H), 6.75 (t, *J* = 7.7 Hz, 1H), 5.68 (d, *J* = 7.7 Hz, 1H), 4.94 (q, *J* = 6.1 Hz, 1H), 4.75 (p, *J* = 8.4 Hz, 1H), 4.44 (ddd, *J* = 7.5, 3.9, 2.3 Hz, 1H), 3.767 (s, 3H), 3.765 (s, 3H), 3.59 (dq, *J* = 10.0, 5.9 Hz, 1H), 3.44 – 3.26 (m, 4H), 3.04 – 3.00 (m, 1H), 3.00 – 2.93 (m, 1H), 2.83 (dt, *J* = 12.4, 8.2 Hz, 1H), 2.53 (dt, *J* = 12.5, 7.9 Hz, 1H), 1.82 (s, 1H), 1.72 (d, *J* = 10.6 Hz, 1H), 1.65 – 1.55 (m, 1H), 1.06 (dq, *J* = 11.6, 9.9 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 150.88; MS (ESI), 812.53 $[M - H]^-$.

[001254] Synthesis of N-(5-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-6-oxo-1,6-dihydropyrimidin-2-yl)acetamide



[001255] To a solution of dry N-[5-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-6-oxo-1H-pyrimidin-2-yl]acetamide (7.0 g, 12.25 mmol) in THF (35 mL) was added triethylamine (4.27 mL, 30.61 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.90 *M* in THF, 24.49 mL, 22.04 mmol) was added dropwise. The water bath was removed. The white slurry was stirred at rt for 2 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (176 μL). Anhydrous $MgSO_4$ (2.35 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 0-60% EtOAc in MeCN (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (8.22 g, 78.5% yield). ^{1}H NMR (600 MHz, DMSO) δ 11.56 (s, 2H), 7.90 – 7.86 (m, 2H), 7.86 – 7.81 (m, 1H), 7.67 – 7.61 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.28 – 7.24 (m, 4H), 7.24 – 7.21 (m, 1H), 6.91 – 6.85 (m, 4H), 4.87 (m, 1H), 4.82 (ddd, *J* = 9.1, 5.9, 3.1 Hz, 1H), 4.59 (m, 1H), 3.85 (td, *J* = 4.5, 2.4 Hz, 1H), 3.77 (dd, *J* = 15.0, 3.1 Hz, 1H), 3.74 (s, 6H), 3.72 – 3.68 (m, 1H), 3.44 (dq, *J* = 11.8, 6.1 Hz, 1H), 3.38 – 3.29 (m, 1H), 3.13 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.04 (dd, *J* = 10.2, 4.7 Hz, 1H), 2.85 – 2.76 (m, 1H), 2.28 – 2.22 (m, 1H), 2.15 (s, 3H), 1.76 (dt, *J* = 12.1, 4.6 Hz, 2H), 1.61 (td, *J* = 13.5, 11.2, 6.2 Hz, 1H), 1.56 – 1.50 (m, 1H), 1.10 (dq, *J* = 11.7, 9.5 Hz, 1H); ^{31}P NMR (243 MHz, DMSO) δ 146.56; MS (ESI), 853.57 $[M - H]^-$.

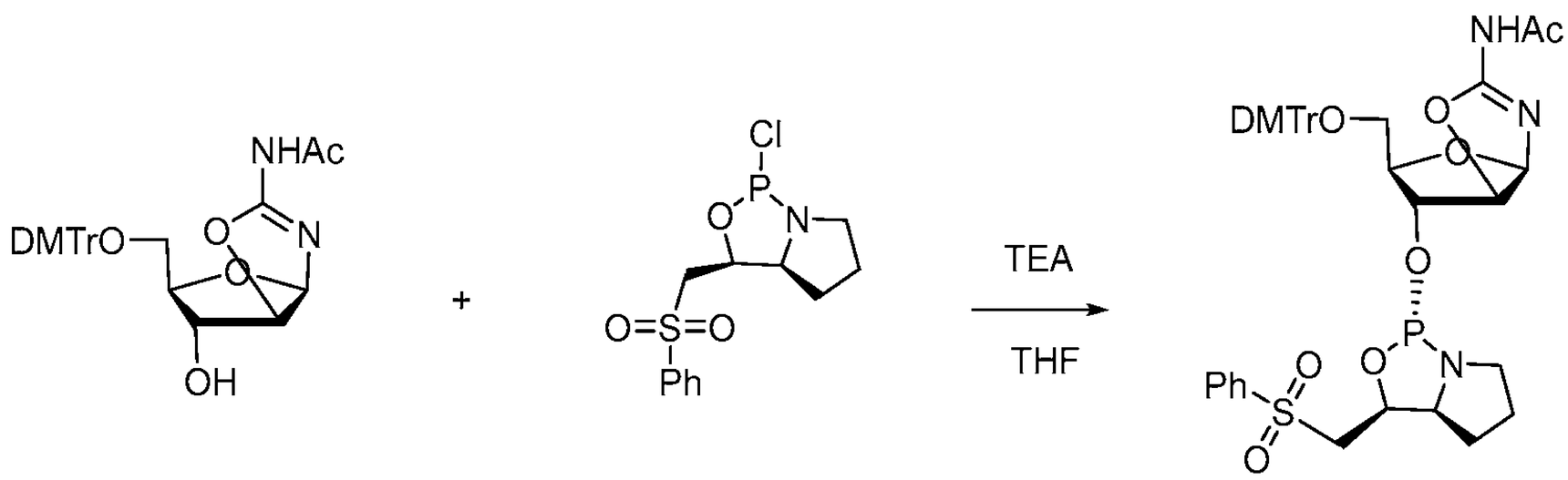
[001256] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione



[001257] To a solution of dry 3-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-1H-pyrimidine-2,4-dione (29.8 g, 56.17 mmol) in THF (200 mL) was added triethylamine (19.57 mL, 140.42 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-

(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.89*M* in THF, 113.59 mL, 101.1 mmol) was added dropwise. The water bath was removed. The cloudy reaction solution was stirred at rt for 2.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (794 μL). Anhydrous $MgSO_4$ (10.6 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 50-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (40.4 g, 88.4% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.28 (bs, 1H), 7.87 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.53 – 7.44 (m, 4H), 7.37 – 7.33 (m, 4H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.81 – 6.75 (m, 4H), 6.70 (dd, *J* = 8.4, 5.1 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.53 (d, *J* = 7.7 Hz, 1H), 4.96 (q, *J* = 6.1 Hz, 1H), 4.87 (dq, *J* = 12.8, 5.6 Hz, 1H), 3.93 (td, *J* = 5.9, 3.9 Hz, 1H), 3.752 (s, 3H), 3.749 (s, 3H), 3.62 (dq, *J* = 11.7, 6.0 Hz, 1H), 3.44 – 3.25 (m, 5H), 2.94 (qd, *J* = 10.0, 4.0 Hz, 1H), 2.85 (ddd, *J* = 13.2, 8.0, 5.2 Hz, 1H), 2.23 (ddd, *J* = 13.6, 8.6, 5.5 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.76 – 1.69 (m, 1H), 1.65 – 1.59 (m, 1H), 1.12 – 1.02 (m, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 149.14; MS (ESI), 812.53 $[M - H]^-$.

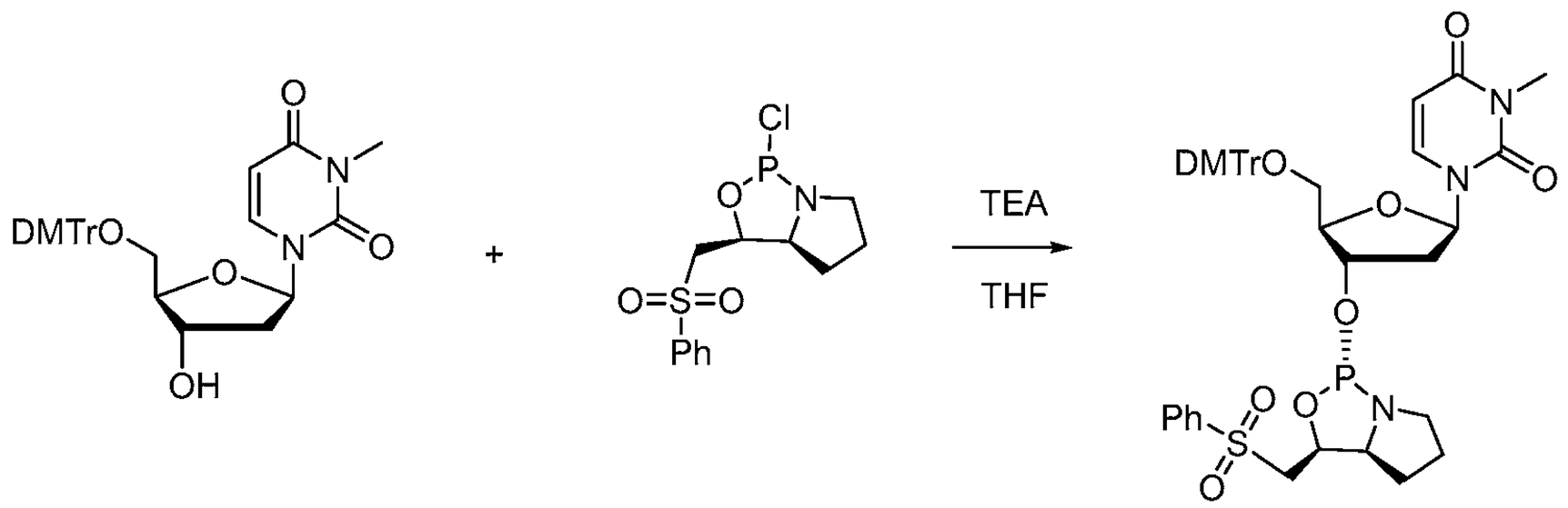
[001258] Synthesis of N-((3aR,5R,6R,6aS)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-6-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl)acetamide



[001259] To a solution of dry N-[(3aR,5R,6aR)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-6-hydroxy-3a,5,6,6a-tetrahydrofuro[2,3-d]oxazol-2-yl]acetamide (4.87 g, 9.38 mmol) in THF (36 mL) was added triethylamine (3.27 mL, 23.45 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.89*M* in THF, 18.97 mL, 16.89 mmol) was added dropwise. The water bath was removed. The resulting cloudy solution was stirred at rt for 1.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (135 μL). Anhydrous $MgSO_4$ (1.8 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 25-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (5.75 g, 76.4% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.93 (dt, *J* = 7.3, 1.3 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.30 – 7.26 (m, 5H), 7.25 (s, 1H), 7.22 – 7.16 (m, 1H), 6.84 – 6.78 (m, 4H), 5.92 (s,

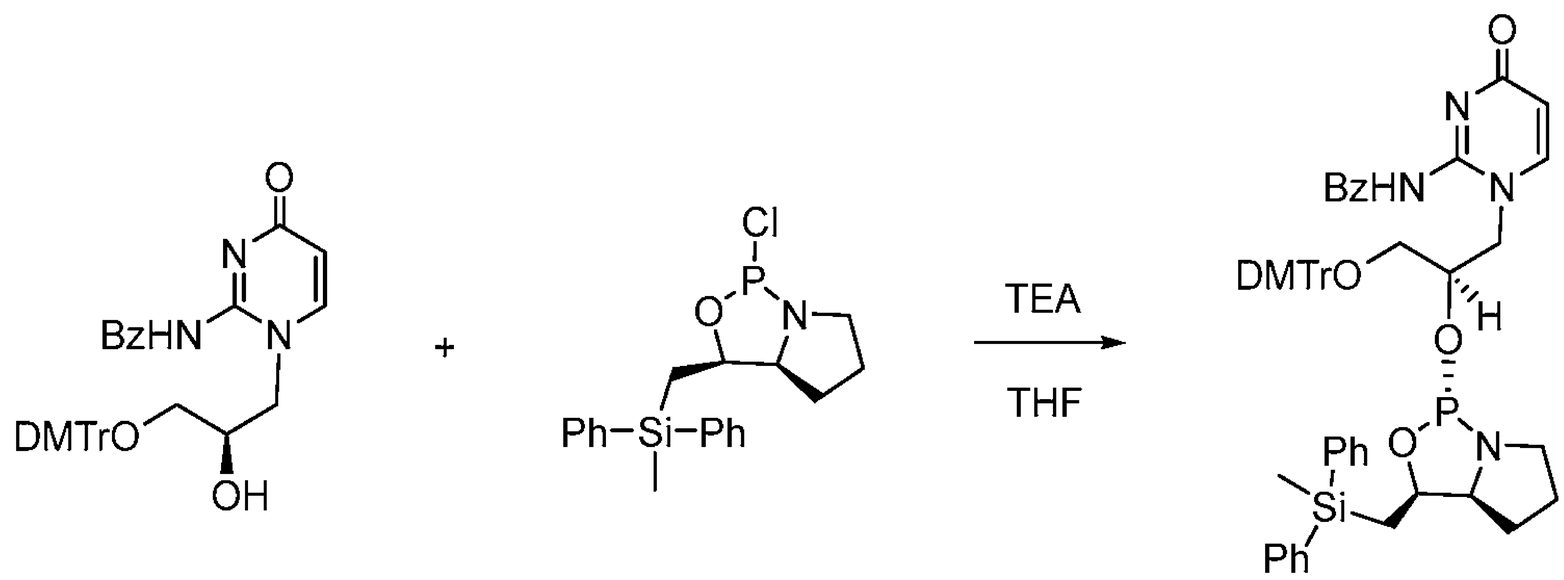
1H), 5.09 (s, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 4.82 – 4.77 (m, 1H), 4.20 (s, 1H), 3.78 (s, 6H), 3.69 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.53 (dd, *J* = 15.5, 5.8 Hz, 1H), 3.47 (dd, *J* = 14.5, 7.3 Hz, 1H), 3.37 (dd, *J* = 14.6, 5.0 Hz, 1H), 3.18 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.13 (s, 1H), 2.93 (dd, *J* = 10.0, 6.8 Hz, 1H), 2.13 (s, 3H), 1.89 (td, *J* = 8.2, 3.9 Hz, 1H), 1.80 (d, *J* = 10.2 Hz, 1H), 1.65 (m, 1H), 1.14 (p, *J* = 9.9 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 152.57; MS (ESI), 802.49 $[M + H]^+$.

[001260] Synthesis of 1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-3-methylpyrimidine-2,4(1H,3H)-dione



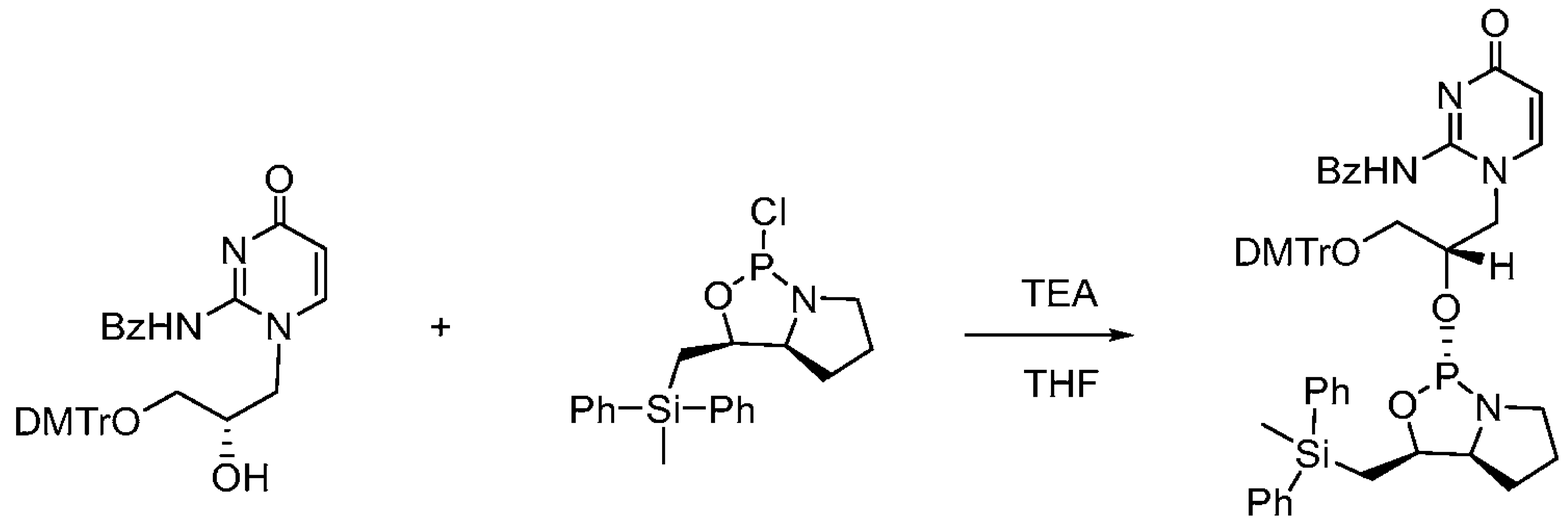
[001261] To a solution of dry 1-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-3-methyl-pyrimidine-2,4-dione (6.2 g, 11.38 mmol) in THF (45 mL) was added triethylamine (3.97 mL, 28.46 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.89*M* in THF, 19.19 mL, 17.08 mmol) was added dropwise. The water bath was removed. The resulting cloudy solution was stirred at rt for 3 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (102 μL). Anhydrous $MgSO_4$ (1.366 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-70% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (7.06 g, 74.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.53 – 7.47 (m, 2H), 7.40 – 7.35 (m, 2H), 7.32 – 7.28 (m, 2H), 7.28 – 7.26 (m, 4H), 7.25 – 7.22 (m, 1H), 6.87 – 6.81 (m, 4H), 6.33 (t, *J* = 6.5 Hz, 1H), 5.42 (d, *J* = 8.1 Hz, 1H), 4.98 (dt, *J* = 6.9, 5.5 Hz, 1H), 4.80 (ddt, *J* = 9.6, 6.7, 3.4 Hz, 1H), 4.02 (q, *J* = 3.1 Hz, 1H), 3.788 (s, 3H), 3.786 (s, 3H), 3.66 – 3.58 (m, 1H), 3.54 – 3.47 (m, 1H), 3.47 – 3.41 (m, 2H), 3.39 – 3.34 (m, 2H), 3.32 (s, 3H), 3.14 (tdd, *J* = 10.3, 8.8, 4.0 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.23 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.88 (td, *J* = 8.4, 4.1 Hz, 1H), 1.79 (q, *J* = 11.4, 10.3 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.15 – 1.06 (m, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 153.80; MS (ESI), 850.35 $[M + Na]^+$.

[001262] Synthesis of N-(1-((R)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-4-oxo-1,4-dihydropyrimidin-2-yl)benzamide



[001263] To a solution of dry N-[1-[(2R)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-4-oxo-pyrimidin-2-yl]benzamide (5.0 g, 8.45 mmol) in THF (37.5mL) was added triethylamine (5.3 mL, 38.03 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 15.89 mL, 15.21 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (122 μL). Anhydrous $MgSO_4$ (1.62 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 10-70% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (5.3 g, 67.4% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.31 (s, 1H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.45 (tdt, *J* = 7.7, 2.7, 1.4 Hz, 7H), 7.37 – 7.26 (m, 12H), 7.24 (ddt, *J* = 10.2, 8.5, 1.6 Hz, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.80 – 6.74 (m, 4H), 5.57 (d, *J* = 8.0 Hz, 1H), 4.71 (dq, *J* = 11.2, 5.8, 4.4 Hz, 2H), 4.40 (dd, *J* = 13.8, 4.0 Hz, 1H), 3.75 (s, 6H), 3.58 (dd, *J* = 13.7, 8.1 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.33 – 3.27 (m, 1H), 3.22 – 3.15 (m, 2H), 2.96 (tdd, *J* = 10.4, 8.5, 5.0 Hz, 1H), 1.74 (qt, *J* = 8.4, 4.1 Hz, 1H), 1.67 - 1.59 (m, 1H), 1.54 (dd, *J* = 14.5, 8.1 Hz, 1H), 1.36 (dd, *J* = 14.6, 7.0 Hz, 1H), 1.32 – 1.26 (m, 1H), 1.24 – 1.17 (m, 1H), 0.52 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 153.11; MS (ESI), 929.76 $[M - H]^-$.

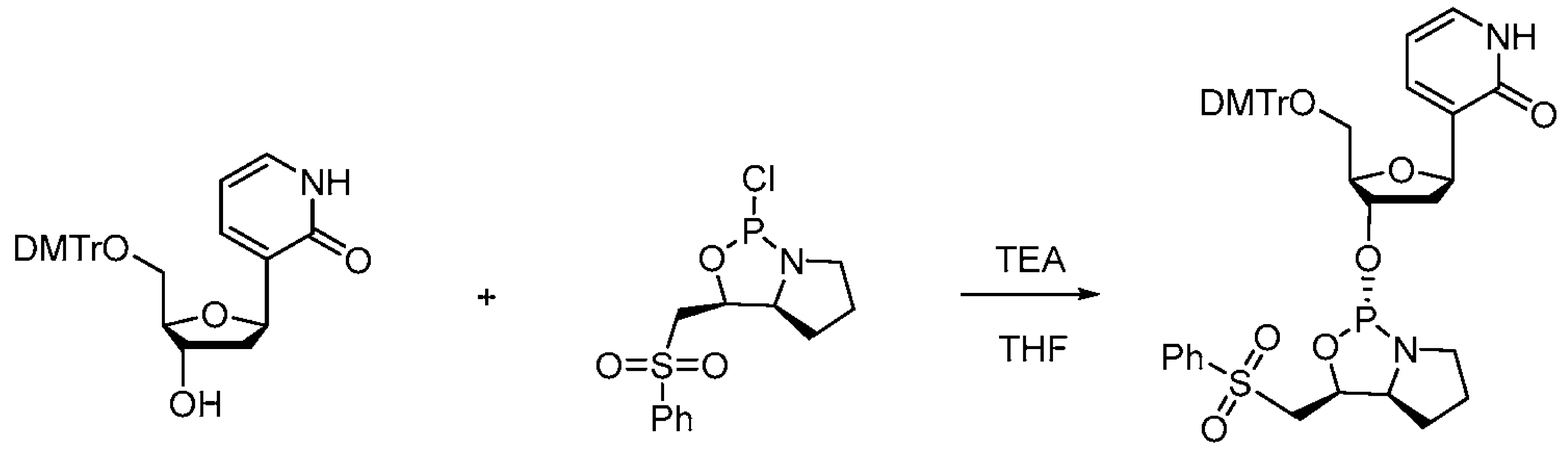
[001264] Synthesis of N-(1-((S)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-4-oxo-1,4-dihydropyrimidin-2-yl)benzamide



[001265] To a solution of dry N-[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-4-oxo-pyrimidin-2-yl]benzamide (7.0 g, 11.83 mmol) in THF (52.5 mL) was added triethylamine (5.94 mL,

42.59 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 22.24 mL, 21.3 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (171 μL). Anhydrous $MgSO_4$ (2.27 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 10-80% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (8.37 g, 76.0% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.34 (s, 1H), 8.25 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.47 (ddt, *J* = 6.7, 2.6, 1.4 Hz, 4H), 7.46 – 7.42 (m, 3H), 7.36 – 7.32 (m, 6H), 7.31 – 7.24 (m, 6H), 7.22 (ddt, *J* = 9.3, 5.3, 1.8 Hz, 3H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.83 – 6.76 (m, 4H), 5.56 (d, *J* = 7.9 Hz, 1H), 4.86 (dd, *J* = 13.6, 3.3 Hz, 1H), 4.70 – 4.60 (m, 2H), 3.75 (s, 6H), 3.42 – 3.30 (m, 3H), 3.20 – 3.12 (m, 1H), 3.09 (dd, *J* = 9.6, 7.4 Hz, 1H), 2.95 – 2.86 (m, 1H), 1.72 (ddt, *J* = 12.7, 8.3, 4.1 Hz, 1H), 1.65 – 1.52 (m, 2H), 1.36 (dd, *J* = 14.6, 6.6 Hz, 1H), 1.31 – 1.24 (m, 1H), 1.14 (dq, *J* = 11.9, 9.5 Hz, 1H), 0.53 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 156.70; MS (ESI), 931.17 $[M + H]^+$.

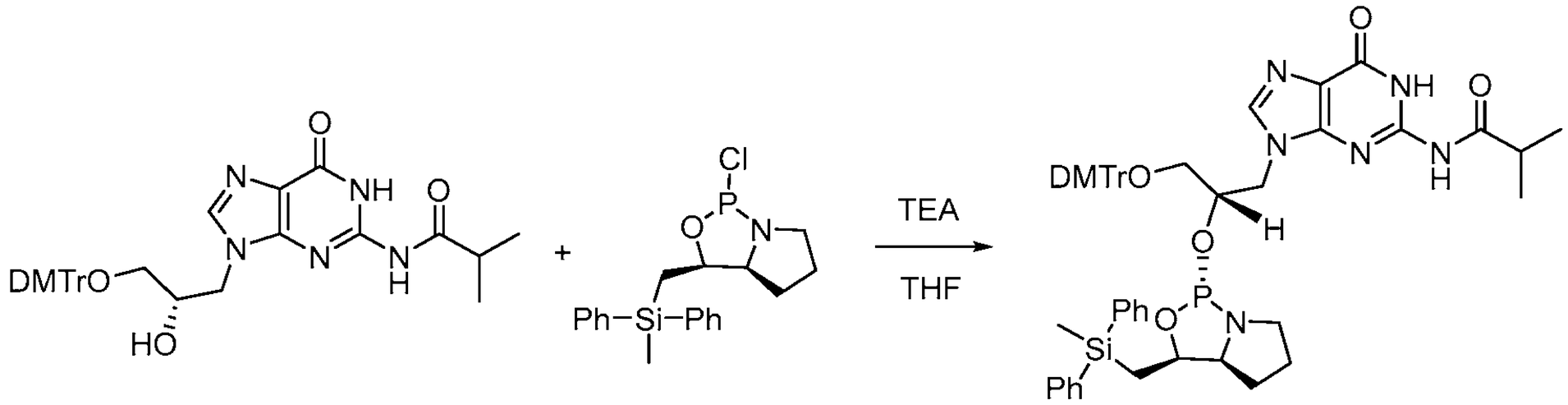
[001266] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)pyridin-2(1H)-one



[001267] To a solution of dry 3-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-1H-pyridin-2-one (4.17 g, 8.12 mmol) in THF (31 mL) was added triethylamine (2.49 mL, 17.86 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.89*M* in THF, 13.68 mL, 12.18 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 2 hr 45 min. The reaction was quenched by water (73 μL). Anhydrous $MgSO_4$ (974 mg) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (3.69 g, 57.0% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.70 (s, 1H), 7.92 – 7.85 (m, 2H), 7.69 (ddd, *J* = 6.9, 2.1, 1.1 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.44 (m, 4H), 7.38 – 7.31 (m, 4H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.25 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.22 – 7.18 (m, 1H), 6.85 – 6.80 (m, 4H), 6.22 (t, *J* = 6.7 Hz, 1H), 5.23 (dd, *J* = 9.9, 5.7 Hz, 1H), 4.94 (q, *J* = 6.0 Hz, 1H), 4.66 (ddd, *J* = 9.1, 6.0, 2.6 Hz, 1H),

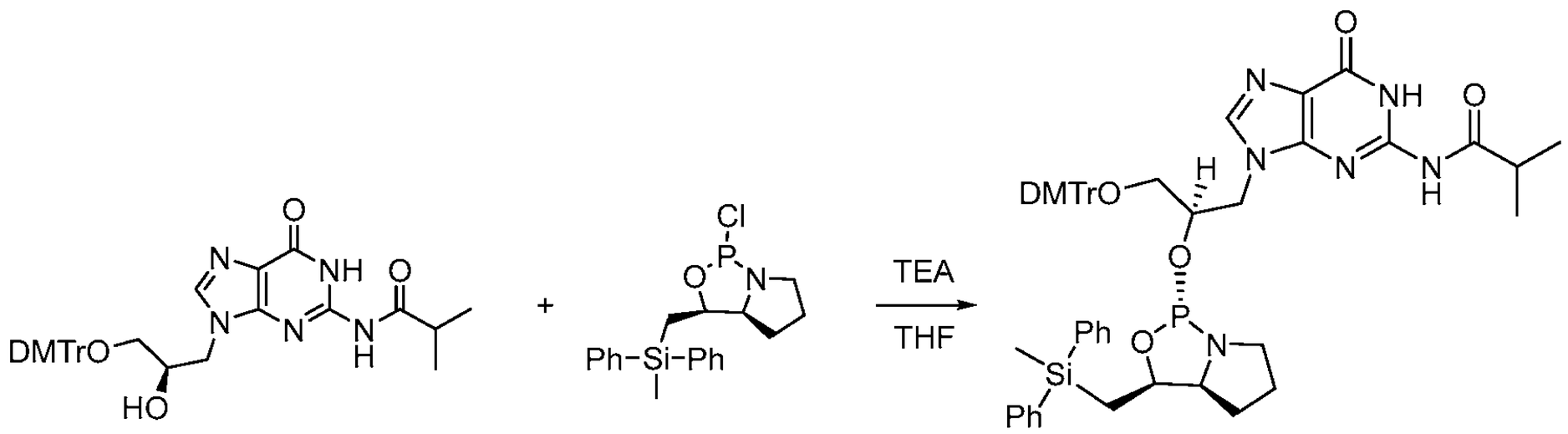
4.04 (q, *J* = 4.1 Hz, 1H), 3.78 (s, 6H), 3.59 (dq, *J* = 11.7, 5.9 Hz, 1H), 3.52 – 3.43 (m, 2H), 3.36 (dd, *J* = 14.6, 5.5 Hz, 1H), 3.29 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.20 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.62 (ddd, *J* = 13.3, 5.8, 2.0 Hz, 1H), 1.86 (ddd, *J* = 13.0, 9.8, 6.2 Hz, 2H), 1.78 – 1.72 (m, 1H), 1.66 – 1.61 (m, 1H), 1.15 – 1.05 (m, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 151.29; MS (ESI), 795.57 $[M - H]^-$.

[001268] Synthesis of N-(9-((S)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide



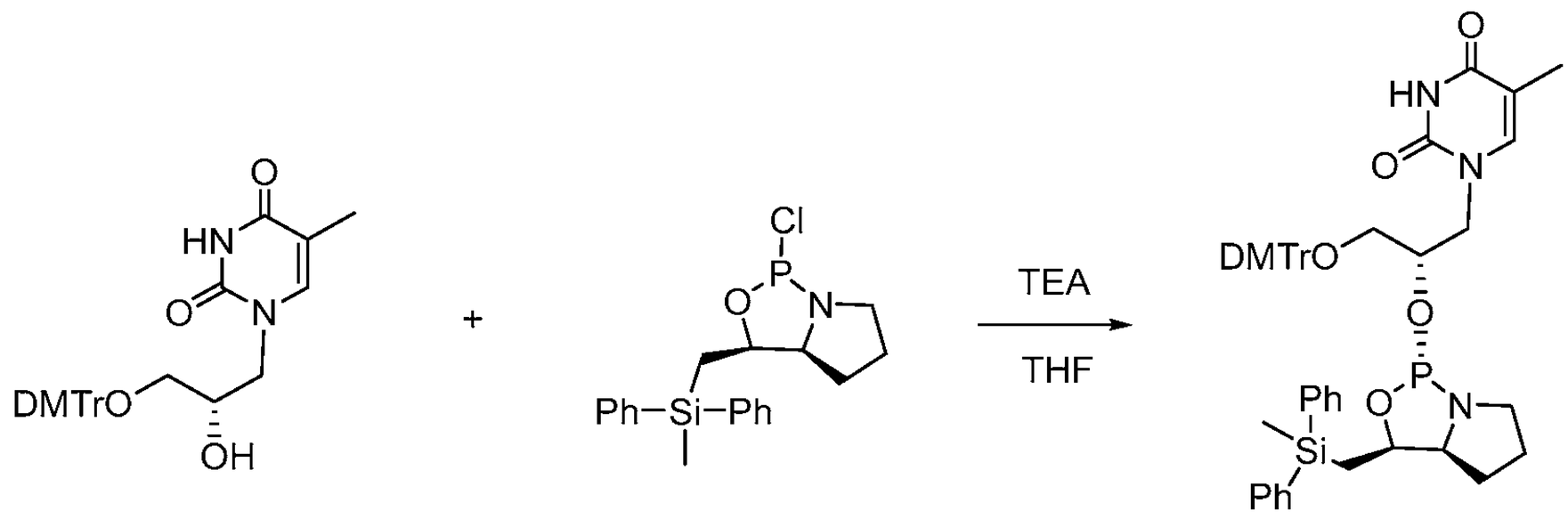
[001269] To a solution of dry N-[9-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-6-oxo-1H-purin-2-yl]-2-methyl-propanamide (6.0 g, 10.04 mmol) in THF (45 mL) was added triethylamine (5.04 mL, 36.14 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 18.87 mL, 18.07 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (144 μL). Anhydrous $MgSO_4$ (1.92 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 25-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (8.18 g, 87.0% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.84 (s, 1H), 7.86 (s, 1H), 7.53 (s, 1H), 7.49 – 7.42 (m, 6H), 7.38 – 7.29 (m, 8H), 7.28 (q, *J* = 3.0, 2.2 Hz, 3H), 7.25 (d, *J* = 1.1 Hz, 1H), 7.23 – 7.19 (m, 1H), 6.83 – 6.78 (m, 4H), 4.73 (dt, *J* = 8.2, 6.2 Hz, 1H), 4.25 – 4.18 (m, 2H), 3.98 (dd, *J* = 14.2, 8.0 Hz, 1H), 3.76 (s, 6H), 3.31 – 3.26 (m, 1H), 3.23 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.22 – 3.16 (m, 1H), 2.94 (dd, *J* = 9.9, 7.1 Hz, 1H), 2.92 – 2.87 (m, 1H), 2.52 (hept, *J* = 6.9 Hz, 1H), 1.71 (dtd, *J* = 12.8, 9.0, 8.4, 4.0 Hz, 1H), 1.61 – 1.52 (m, 2H), 1.37 (dd, *J* = 14.6, 6.6 Hz, 1H), 1.30 – 1.22 (m, 7H), 1.10 (dq, *J* = 11.9, 9.7 Hz, 1H), 0.53 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 156.67; MS (ESI), 935.73 $[M - H]^-$.

[001270] Synthesis of N-(9-((R)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide



[001271] To a solution of dry N-[9-[(2R)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-6-oxo-1H-purin-2-yl]-2-methyl-propanamide (5.5 g, 9.2 mmol) in THF (41 mL) was added triethylamine (4.62 mL, 33.13 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 17.3 mL, 16.56 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (132 μL). Anhydrous $MgSO_4$ (2.27 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 40-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (6.265 g, 72.6% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.81 (s, 1H), 7.78 (s, 1H), 7.53 (ddd, *J* = 7.7, 3.8, 2.0 Hz, 4H), 7.42 – 7.38 (m, 3H), 7.36 – 7.31 (m, 3H), 7.31 – 7.27 (m, 3H), 7.27 – 7.24 (m, 6H), 7.21 – 7.17 (m, 1H), 6.81 – 6.74 (m, 4H), 4.74 (dt, *J* = 8.5, 6.2 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.00 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.87 (dd, *J* = 14.1, 4.4 Hz, 1H), 3.769 (s, 3H), 3.768 (s, 3H), 3.43 (ddt, *J* = 14.7, 10.7, 7.6 Hz, 1H), 3.31 (ddt, *J* = 9.6, 7.3, 5.6 Hz, 1H), 3.08 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.00 (tdd, *J* = 10.9, 8.7, 4.5 Hz, 1H), 2.90 (dd, *J* = 9.9, 5.8 Hz, 1H), 2.47 (hept, *J* = 6.9 Hz, 1H), 1.78 (ddt, *J* = 16.2, 8.0, 3.2 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.40 (dd, *J* = 14.6, 6.5 Hz, 1H), 1.38 – 1.30 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.21 – 1.16 (m, 1H), 0.65 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 155.34; MS (ESI), 937.91 $[M + H]^+$.

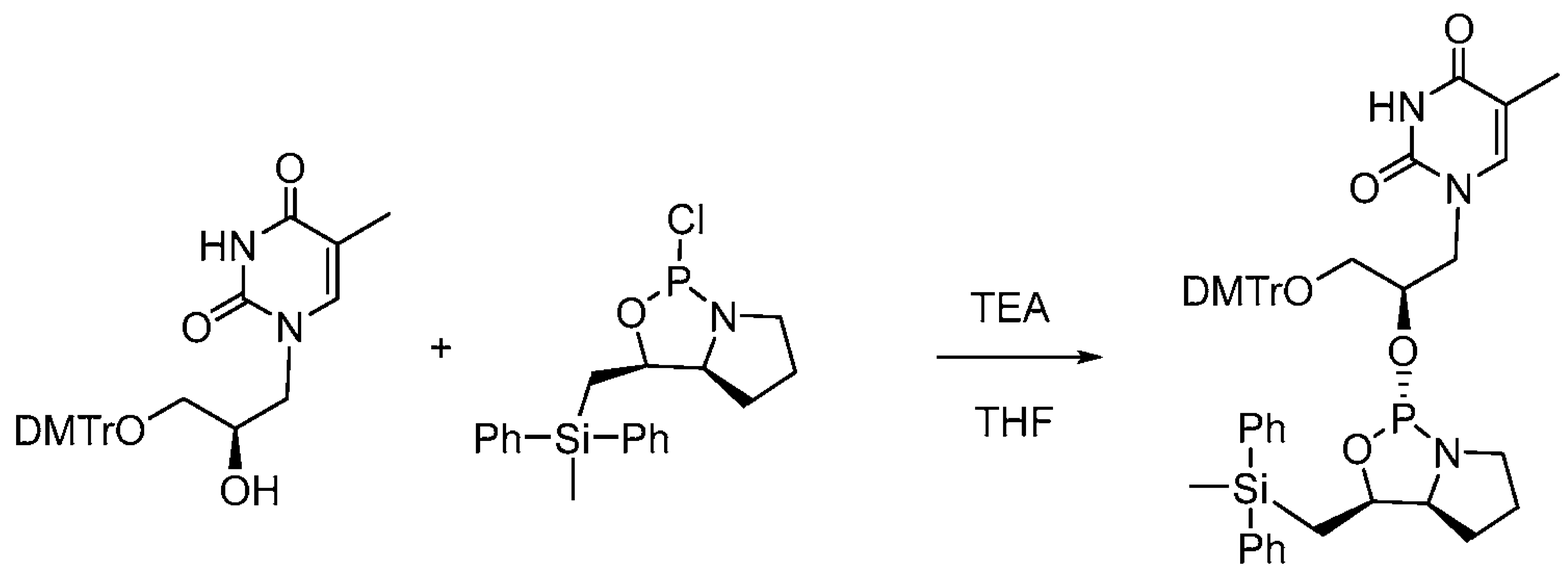
[001272] Synthesis of 1-((S)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-5-methylpyrimidine-2,4(1H,3H)-dione



[001273] To a solution of dry 1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-5-

methyl-pyrimidine-2,4-dione (6.0 g, 11.94 mmol) in THF (45 mL) was added triethylamine (4.99 mL, 35.82 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 22.45 mL, 21.49 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (172 μL). Anhydrous $MgSO_4$ (2.29 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 10-80% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (8.26 g, 82.2% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.48 (dt, *J* = 6.7, 1.4 Hz, 4H), 7.47 – 7.44 (m, 2H), 7.39 – 7.30 (m, 7H), 7.30 – 7.26 (m, 5H), 7.23 – 7.17 (m, 1H), 6.87 (d, *J* = 1.4 Hz, 1H), 6.85 – 6.79 (m, 4H), 4.77 (dt, *J* = 8.5, 5.9 Hz, 1H), 4.38 – 4.29 (m, 1H), 4.16 (dd, *J* = 14.1, 3.6 Hz, 1H), 3.76 (s, 6H), 3.41 (tdd, *J* = 14.5, 9.4, 7.2 Hz, 1H), 3.31 (dd, *J* = 14.0, 8.9 Hz, 1H), 3.26 – 3.18 (m, 1H), 3.15 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.08 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.00 – 2.92 (m, 1H), 1.81 – 1.73 (m, 1H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.62 (qt, *J* = 11.0, 5.1 Hz, 1H), 1.56 (dd, *J* = 14.6, 8.6 Hz, 1H), 1.37 (dd, *J* = 14.6, 6.3 Hz, 1H), 1.32 (qd, *J* = 7.4, 3.0 Hz, 1H), 1.19 (dq, *J* = 12.1, 9.5 Hz, 1H), 0.56 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 155.31; MS (ESI), 840.68 $[M - H]^-$.

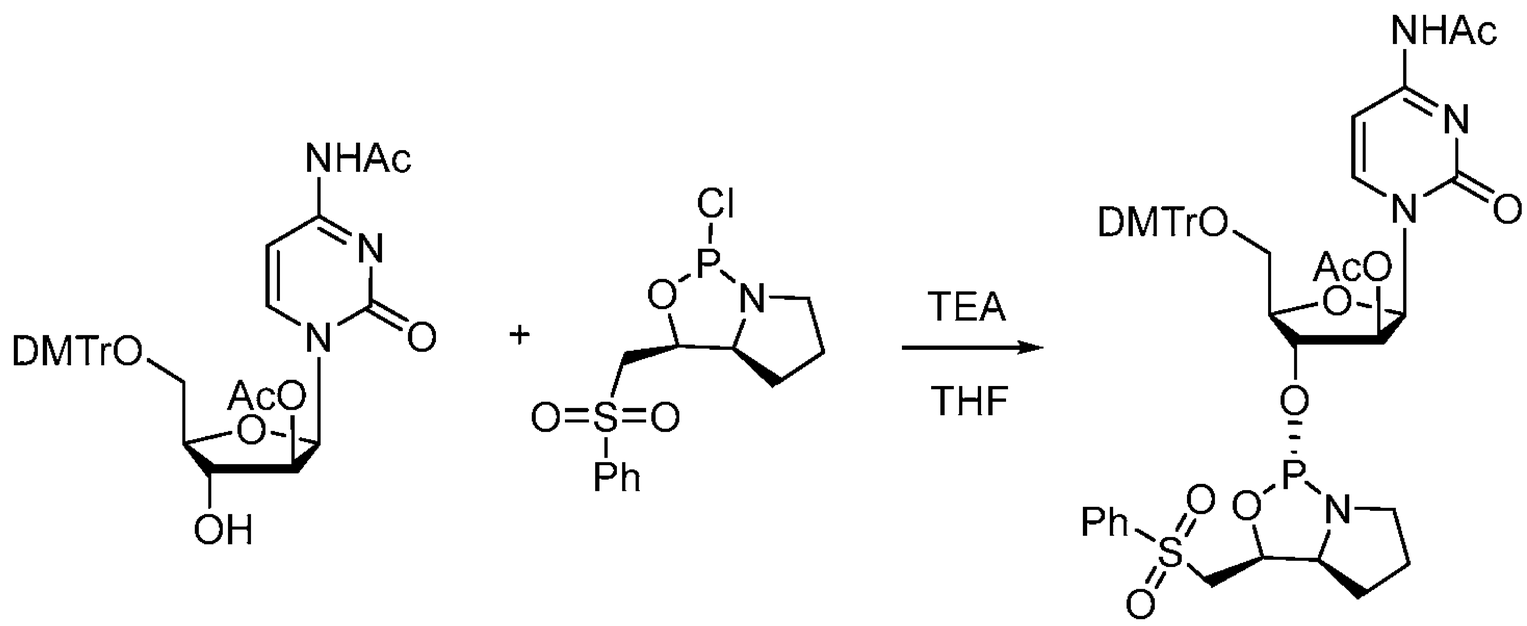
[001274] Synthesis of 1-((R)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((methyldiphenylsilyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-5-methylpyrimidine-2,4(1H,3H)-dione



[001275] To a solution of dry 1-[(2R)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-5-methyl-pyrimidine-2,4-dione (5.54 g, 11.02 mmol) in THF (41.6 mL) was added triethylamine (4.61 mL, 33.07 mmol). The flask was set in a water bath. [(3S,3aS)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-3-yl]methyl-methyl-diphenyl-silane (0.9574*M* in THF, 20.73 mL, 19.84 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (159 μL). Anhydrous $MgSO_4$ (2.115 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (7.63 g, 82.2% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ

8.17 (s, 1H), 7.48 (dt, *J* = 8.0, 1.6 Hz, 4H), 7.45 – 7.42 (m, 2H), 7.36 – 7.24 (m, 12H), 7.23 – 7.17 (m, 1H), 6.93 (q, *J* = 1.2 Hz, 1H), 6.84 – 6.77 (m, 4H), 4.74 (dt, *J* = 8.5, 6.1 Hz, 1H), 4.36 – 4.28 (m, 1H), 3.85 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.54 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.49 – 3.40 (m, 1H), 3.40 – 3.34 (m, 1H), 3.16 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.03 (dd, *J* = 10.1, 4.4 Hz, 1H), 2.99 – 2.90 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.78 – 1.72 (m, 1H), 1.68 – 1.58 (m, 1H), 1.54 (dd, *J* = 14.6, 8.5 Hz, 1H), 1.42 – 1.31 (m, 2H), 1.26 – 1.21 (m, 1H), 0.59 (s, 3H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 151.30; MS (ESI), 840.78 $[M - H]^-$.

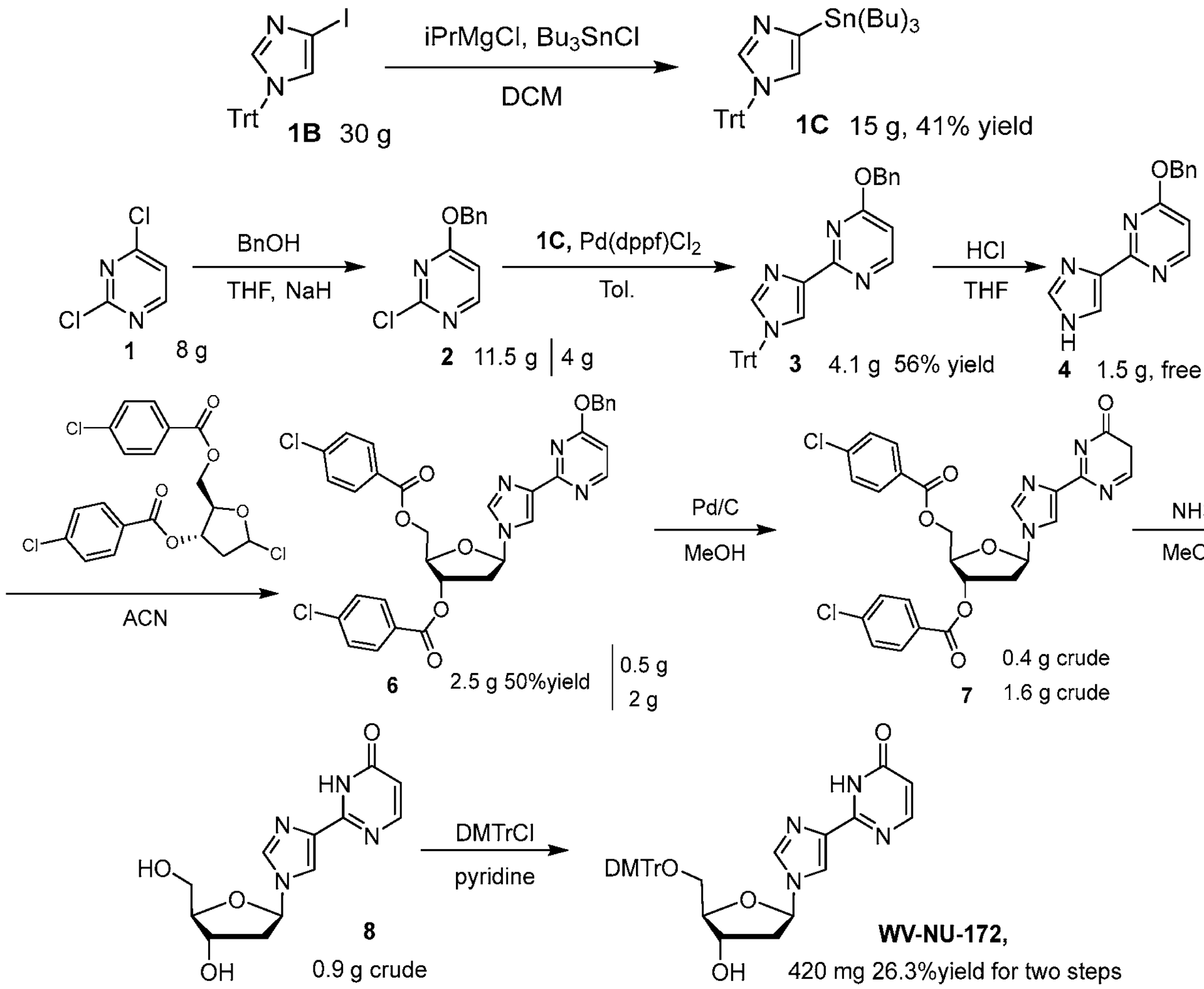
[001276] Synthesis of (2R,3S,4R,5R)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-3-yl acetate



[001277] To a solution of dry [(2R,3R,5R)-2-(4-acetamido-2-oxo-pyrimidin-1-yl)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-3-yl] acetate (10.0 g, 15.88 mmol) in THF (75 mL) was added triethylamine (4.87 mL, 34.94 mmol). The rxn flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.43*M* in THF, 55.4 mL, 23.82 mmol) was added dropwise. The water bath was removed. The resulting cloudy reaction solution was stirred at rt for 1.5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (143 μL). Anhydrous $MgSO_4$ (1.906 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (9.35 g, 64.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.93 – 7.89 (m, 2H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.38 – 7.33 (m, 4H), 7.31 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 6.88 – 6.83 (m, 4H), 6.31 (d, *J* = 4.1 Hz, 1H), 5.44 (dd, *J* = 4.2, 2.1 Hz, 1H), 5.04 (q, *J* = 6.1 Hz, 1H), 4.58 (ddd, *J* = 9.2, 3.6, 2.2 Hz, 1H), 4.14 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.79 (s, 6H), 3.65 (dq, *J* = 9.9, 6.0 Hz, 1H), 3.54 – 3.43 (m, 2H), 3.42 – 3.31 (m, 3H), 3.13 – 3.04 (m, 1H), 2.26 (s, 3H), 1.87 (dtd, *J* = 16.8, 8.1, 4.0 Hz, 1H), 1.81 (s, 3H), 1.80 – 1.71 (m, 1H), 1.64 (ddt, *J* = 12.0, 7.4, 4.2 Hz, 1H), 1.10 (dtd, *J* = 11.7, 10.0, 8.5 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 153.43; MS (ESI), 913.46 $[M + H]^+$.

[001278] Synthesis of WV-NU-172 and amidtes.

[001279] In some embodiments, WV-NU-172 was prepared as below:



[001280] In some embodiments, WV-NU-172 was prepared as below at a difference scale:

[001281] For two batches: To a solution of compound 1B (60 g, 137.52 mmol, 1 *eq.*) in DCM (1200 mL), and chloro(isopropyl)magnesium (2 M, 103.14 mL, 1.5 *eq.*) was added at 20°C, after 1hr and then tributyl(chloro)stannane (66.70 g, 204.91 mmol, 55.12 mL, 1.49 *eq.*) was added slowly and the mixture was stirred at 20°C for 12hr. TLC (Petroleum ether: Ethyl acetate = 3:1) showed the compound 1B was consumed. The two batches were combined for work up. The reaction mixture was quenched by the addition of water (500 mL) carefully and the mixture was extracted with DCM (500 mL×2). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 10/1, 3/1) to get compound 1C (120 g, 200.19 mmol, 72.78% yield) as a white solid. TLC: (Petroleum ether: Ethyl acetate = 3:1), Rf = 0.25.

[001282] t-BuOK (79.09 g, 704.80 mmol, 1.05 *eq.*) was added to a solution of BnOH (145.18 g, 1.34 mol, 139.59 mL, 2 *eq.*) in THF (500 mL) and stirred until dissolved. This mixture was added dropwise to a solution of compound 1 (100 g, 671.24 mmol, 1 *eq.*) in DMF (500 mL) cooled to -78 °C under an inert atmosphere. The mixture was allowed to warm slowly to 20 °C, and stirred for 1h. TLC (Petroleum ether: Ethyl acetate = 3:1, Rf = 0.76) indicated compound 1 was consumed completely and one main new spot formed. The reaction mixture was diluted with H2O 1000 mL and extracted with EtOAc mL (500 mL * 2). The combined organic

layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to get compound 2 (80 g, 362.56 mmol, 54.01% yield) was obtained as a white solid. TLC: (Petroleum ether: Ethyl acetate = 3:1), Rf = 0.76.

[001283] To a solution of compound 1C (85.57 g, 142.76 mmol, 1.26 *eq.*) in toluene (900 mL) was added 4-benzyloxy-2-chloro-pyrimidine (25 g, 113.30 mmol, 1 *eq.*), $Pd(dppf)Cl_2.CH_2Cl_2$ (9.25 g, 11.33 mmol, 0.1 *eq.*). The mixture was stirred at 120 °C for 3 hr under N_2. TLC (Petroleum ether: Ethyl acetate = 1:1) showed the reactant 1 was consumed and the new spots was found. The mixture was concentrated to get the crude. The mixture was purified by MPLC (SiO_2, Petroleum ether/Ethyl acetate = 10:1, 5:1) to get compound 3 (45 g, 90.99 mmol, 80.31% yield) as a brown solid. TLC: (Petroleum ether: Ethyl acetate = 1:1), Rf = 0.24.

[001284] To a solution of compound 3 (45 g, 90.99 mmol, 1 *eq.*) in THF (400 mL) was added HCl (5 M, 90.99 mL, 5 *eq.*). The mixture was stirred at 15 °C for 2 hr. TLC (Petroleum ether: Ethyl acetate = 0:1) showed the desired substance was detected. The reaction mixture was diluted with water 50 mL and extracted with EtOAc 90 mL (30mL * 3). The combined water layers were added 2N NaOH aq until pH>11, and extracted with DCM (50 mL*3), the combined organic was dried over Na_2SO_4, filtered and concentrated to get the compound 4 (23 g, crude) was obtained as a yellow solid. TLC (Petroleum ether: Ethyl acetate = 0:1), Rf = 0.01.

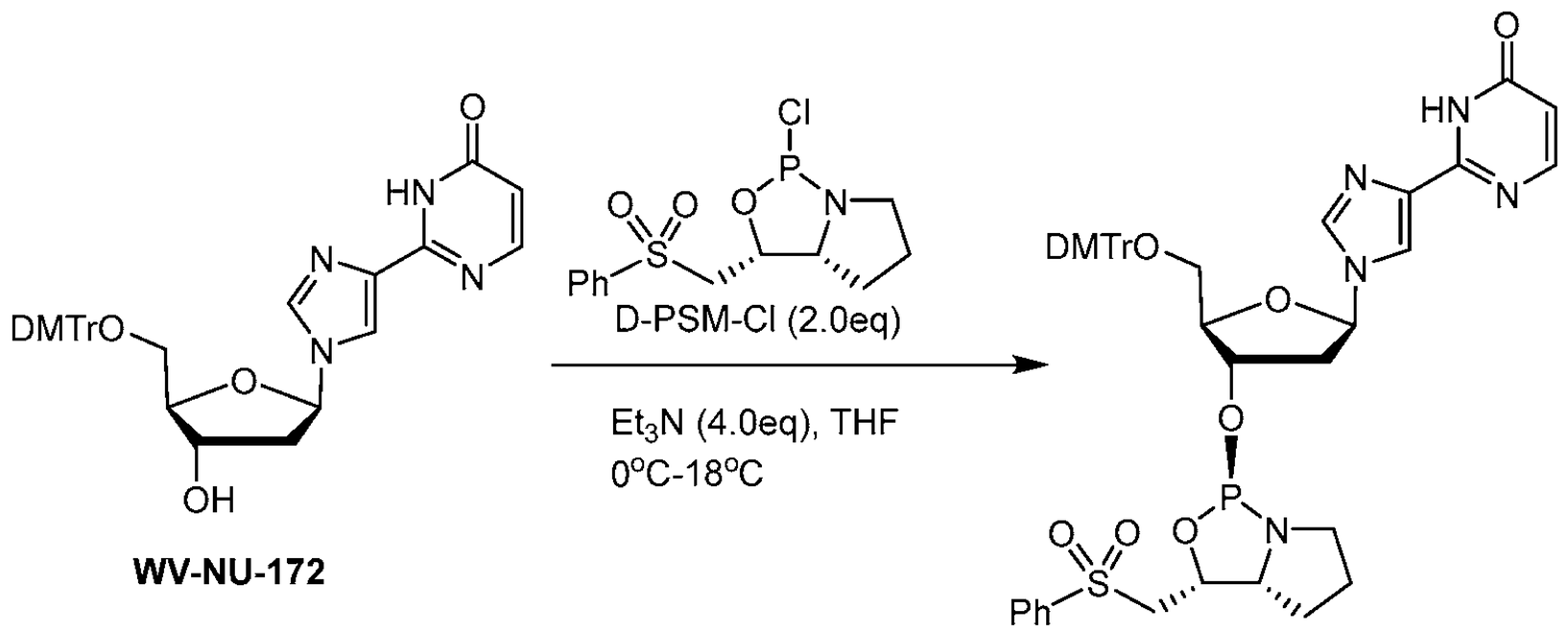
[001285] To a solution of compound 4 (23 g, 91.17 mmol, 1 *eq.*) in MeCN (800 mL) was added NaH (7.29 g, 182.34 mmol, 60% purity, 2 *eq.*), the mixture was stirred at 0 °C for 30 min, then compound 1E (47.01 g, 109.41 mmol, 1.2 *eq.*) was added. The mixture was stirred at 15 °C for 12 hr. LCMS showed the compound 4 was consumed and the desired substance was found. The reaction mixture filtered, and the cake was washed with DCM (100 mL), concentrated the filtrate to get the crude. The mixture was purified by MPLC (SiO_2, DCM: MeOH = 20:1) to get compound 6 (30 g, crude) as a yellow oil. LCMS: (M+H+): 645.3. TLC (DCM: MeOH = 20:1), Rf = 0.24.

[001286] To a solution of compound 6 (30 g, 46.48 mmol, 1 *eq.*) in MeOH (600 mL) was added Pd/C (6, 46.48 mmol, 10% purity, 1 *eq.*) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 15 °C for 12 hr. LCMS showed the compound 6 was consumed and the desired mass was found. The mixture was filtered and concentrated to get the compound 7 (25 g, crude) as a yellow oil. LCMS: (M+H+): 555.2.

[001287] To a solution of compound 7 (2 g, 3.60 mmol, 1 *eq.*.) in AMMONIA (200 mL), the mixture was stirred at 15 °C for 12 hr. LCMS showed the compound 7 was consumed. The mixture was concentrated to get the compound 8 (1 g, 3.59 mmol, 99.79% yield) as s yellow oil. To a solution of compound 7 (25 g, 45.02 mmol, 1 *eq.*) in ammonia (1000 mL), the mixture was stirred at 15 °C for 12 hr. LCMS showed the compound 7 was consumed. The mixture was concentrated to get the crude. The mixture was purified by MPLC(SiO2,Dichloromethane : Methanol = 20; 1,10:1,5:1) to get compound 8 (11 g, 39.53 mmol, 87.82% yield) as s yellow oil. LCMS: (M+H+): 279.1. TLC: (Dichloromethane: Methanol = 10:1), Rf = 0.15.

[001288] To a solution of compound 8 (5 g, 17.97 mmol, 1 *eq.*) in pyridine (60 mL), and DMTCl (6.39 g, 18.87 mmol, 1.05 *eq.*) was added to the mixture, the solution was stirred at 20°C for 1.5 hr. LCMS showed the compound 8 was consumed and the desired substance was found. MeOH (10 mL) was added to the mixture and concentrated to get the crude. The mixture was purified by Pre-HPLC (column: Phenomenex C18 250*70mm 10u;mobile phase: [water(NH_4HCO_3)-ACN];B%: 40%-65%,20min) to get WV-NU-172 (2.5 g, 4.31 mmol, 23.96% yield) as a yellow solid. ^{1}HNMR (400 MHz, DMSO-d6) δ = 11.74 (br s, 1H), 8.23 - 8.03 (m, 2H), 7.97 - 7.80 (m, 1H), 7.39 - 7.33 (m, 2H), 7.31 - 7.16 (m, 7H), 6.85 (br dd, J = 5.4, 8.5 Hz, 4H), 6.17 (br t, J = 6.0 Hz, 2H), 5.39 (br d, J = 4.1 Hz, 1H), 4.33 (br s, 1H), 3.96 (br d, J = 3.8 Hz, 1H), 3.71 (d, J = 3.8 Hz, 6H), 3.17 - 3.12 (m, 2H), 2.42 - 2.22 (m, 1H). LCMS: (M-H+): 579.3.

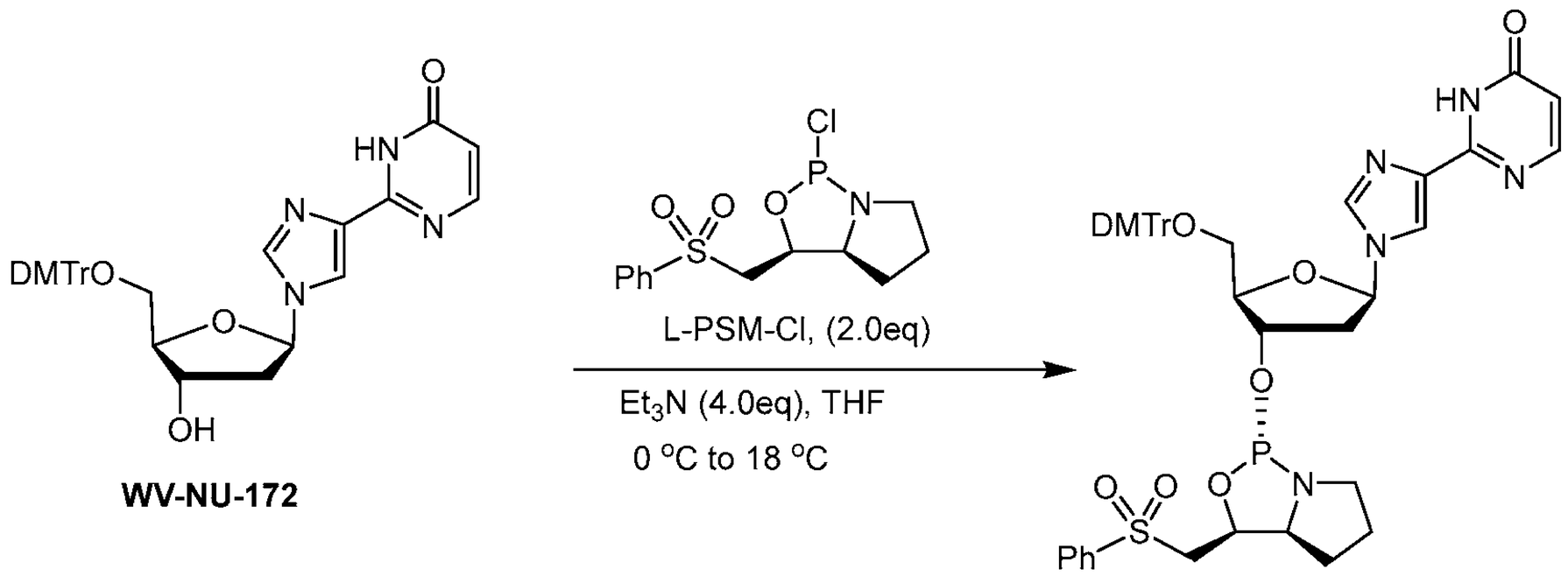
[001289] Amidites of WV-NU-172 can be prepared using various technologies in accordance with the present disclosure. For example, in some embodiments amidites are prepared as described below.



WV-NU-172

[001290] Nucleosides WV-NU-172 (1.9 g, 3.27 mmol, 1.0 eq.) in an 250 mL size three necked flask was azeotroped with anhydrous toluene (30 mL) and was dried for 48 hrs on high vacuum. To the flask was added anhydrous THF (10 mL) under argon and solution was cooled to -10°C. to the reaction mixture was added triethyl amine (4.0 eq.) followed by addition of D-PSM-Cl (0.9 M) solution (2.0 eq.) over the period of 10 min. The reaction mixture was warmed to room temperature and reaction progress was monitored by HPLC. After disappearance of starting material, reaction was quenched by addition of water and dried by addition of molecular sieve. The reaction mixture was filtered through fritted glass tube. Reaction flask and precipitate was washed with anhydrous THF (25 mL). Obtained filtrate was collected and solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO2, 40-100% Ethyl acetate in Hexanes) to give D-PSM-WV-NU-172 Amidite off white solid (1.6 g, 57% yield). ^{31}P NMR (243 MHz, $CDCl_3$) δ = 154.34. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 3H), 7.86 (d, *J* = 1.4 Hz, 1H), 7.71 (d, *J* = 1.4 Hz, 1H), 7.62 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.43 – 7.38 (m, 2H), 7.34 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 6.85 (ddq, *J* = 8.4, 3.1, 1.8 Hz, 4H), 6.31 (dd, *J* = 6.6, 1.4 Hz, 1H), 6.04 (dd, *J* = 7.9, 5.5 Hz, 1H), 5.07 (dt, *J* = 7.4, 5.5 Hz, 1H), 4.79 (ddd, *J* = 8.2, 5.3, 2.5 Hz, 1H), 4.18 (td, *J* = 4.2, 2.2 Hz, 1H), 3.82 – 3.74 (m, 8H), 3.68 (ddd, *J* = 9.7, 5.5, 2.7 Hz, 1H), 3.58 – 3.47 (m, 2H), 3.40 (dd, *J* = 14.4, 5.3 Hz, 1H), 3.30 (qd, *J* = 10.4, 4.2 Hz, 2H), 3.20 (ddd, *J* = 10.3, 4.0, 1.6 Hz, 1H), 2.56 (ddd, *J* = 13.5, 5.6, 2.3 Hz, 1H), 2.47 (ddd, *J* = 13.6, 8.0, 5.8 Hz, 1H), 1.96 – 1.81 (m, 4H), 1.72 – 1.65 (m, 1H), 1.18 – 1.11 (m, 1H). ^{13}C NMR (151

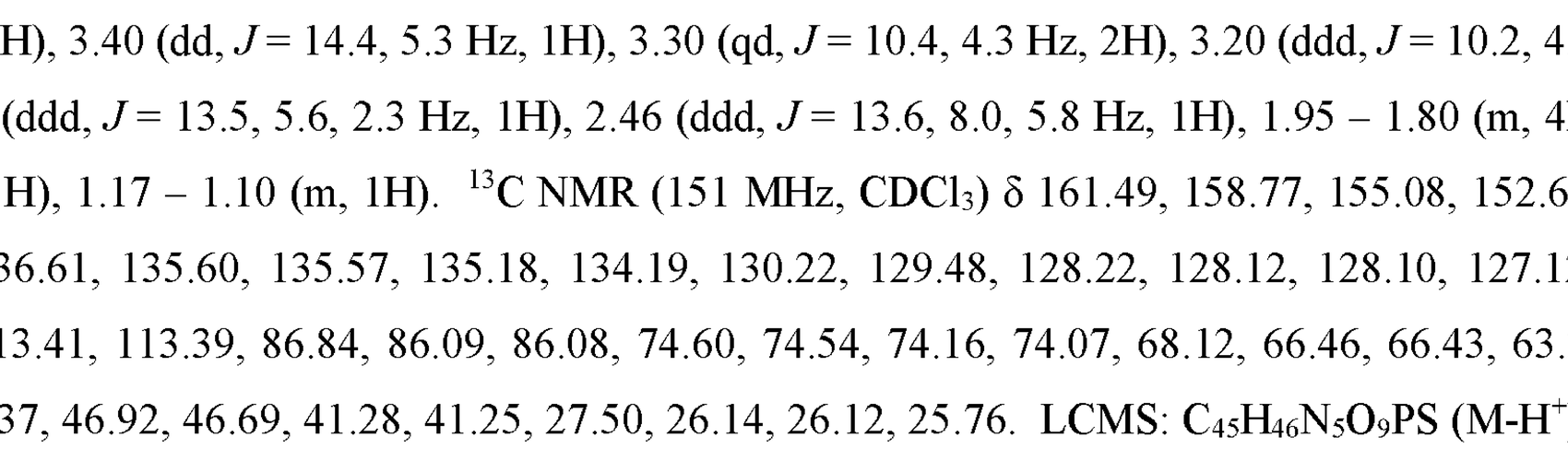
MHz, $CDCl_3$) δ 161.36, 158.64, 154.95, 152.50, 144.40, 139.41, 136.49, 135.47, 135.45, 135.06, 134.06, 130.09, 130.01, 129.35, 128.10, 128.03, 127.99, 127.97, 126.99, 119.43, 113.68, 113.28, 113.26, 86.71, 85.97, 85.95, 74.47, 74.41, 74.03, 73.94, 67.99, 66.33, 66.31, 63.12, 58.01, 57.99, 55.25, 46.79, 46.56, 41.15, 41.12, 27.37, 26.01, 25.99, 25.63. LCMS: $C_{45}H_{46}N_5O_9PS$ ($M\text{-}H^+$): 865.04.



WV-NU-172

[001291] Nucleosides WV-NU-172 (0.9 g) was converted to L-PSM-WV-NU-172 Amidite (510 mg, 45% yield) as an off-white solid. ^{31}P NMR (243 MHz, $CDCl_3$) δ = 153.78. ^1H NMR (600 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 3H), 7.86 (d, *J* = 1.5 Hz, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.62 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 6.85 (ddq, *J* = 8.4, 3.1, 1.8 Hz, 4H), 6.31 (dd, *J* = 6.6, 1.3 Hz, 1H), 6.03 (dd, *J* = 7.9, 5.4 Hz, 1H), 5.07 (dt, *J* = 7.4, 5.5 Hz, 1H), 4.79 (ddd, *J* = 8.2, 5.3, 2.5 Hz, 1H), 4.19 (td, *J* = 4.2, 2.2 Hz, 1H), 3.82 – 3.72 (m, 8H), 3.68 (ddd, *J* = 9.7, 5.5, 2.7 Hz, 1H), 3.58 – 3.47 (m, 2H), 3.40 (dd, *J* = 14.4, 5.3 Hz, 1H), 3.30 (qd, *J* = 10.4, 4.3 Hz, 2H), 3.20 (ddd, *J* = 10.2, 4.0, 1.6 Hz, 1H), 2.56 (ddd, *J* = 13.5, 5.6, 2.3 Hz, 1H), 2.46 (ddd, *J* = 13.6, 8.0, 5.8 Hz, 1H), 1.95 – 1.80 (m, 4H), 1.72 – 1.64 (m, 1H), 1.17 – 1.10 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.49, 158.77, 155.08, 152.63, 144.53, 139.54, 136.61, 135.60, 135.57, 135.18, 134.19, 130.22, 129.48, 128.22, 128.12, 128.10, 127.12, 119.56, 113.81, 113.41, 113.39, 86.84, 86.09, 86.08, 74.60, 74.54, 74.16, 74.07, 68.12, 66.46, 66.43, 63.25, 58.14, 58.12, 55.37, 46.92, 46.69, 41.28, 41.25, 27.50, 26.14, 26.12, 25.76. LCMS: $C_{45}H_{46}N_5O_9PS$ ($M\text{-}H^+$): 865.04.

[001292] Synthesis of N-(1-((S)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide

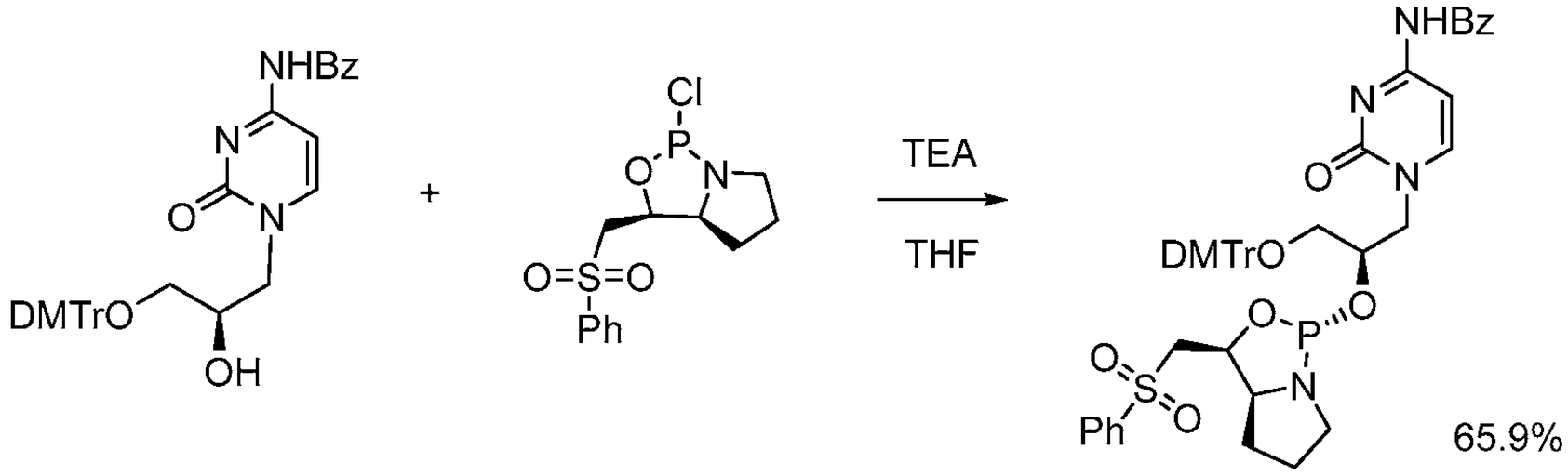


79.5%

[001293] To a solution of dry N-[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-2-oxo-pyrimidin-4-yl]benzamide (4.79 g, 8.1 mmol) in THF (48 mL) was added triethylamine (6.1 mL, 43.73

mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.9*M* in THF, 16.2 mL, 14.58 mmol) was added dropwise. The off-white slurry was stirred at rt for 7 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (146 uL). Anhydrous $MgSO_4$ (1.94 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 5% triethylamine) as the gradient to afford the title compound as a light-brown foam (5.63 g, 79.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (bs, 1H), 7.93 – 7.86 (m, 2H), 7.85 – 7.81 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.56 (tt, J = 7.6, 1.2 Hz,, 1H), 7.51 (tt, J = 7.9, 1.6 Hz, 2H), 7.47 (dt, J = 7.1, 1.5 Hz, 2H), 7.42 (tt, J = 8.1, 1.6 Hz, 3H), 7.35 (dd, J = 8.9, 2.1 Hz, 4H), 7.30 (t, J = 7.7 Hz, 3H), 7.21 (tt, J = 7.4, 1.3 Hz, 1H), 6.85 (dd, J = 8.9, 1.5 Hz, 4H), 5.09 (q, J = 6.3 Hz, 1H), 4.59 – 4.52 (m, 1H), 4.41 (dd, J = 13.4, 3.3 Hz, 1H), 3.79 (s, 6H), 3.71 – 3.62 (m, 1H), 3.57 (dd, J = 13.4, 9.1 Hz, 1H), 3.43 (dd, J = 14.3, 6.8 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.30 (dd, J = 14.6, 6.1 Hz, 1H), 3.18 (qd, J = 9.9, 4.7 Hz, 2H), 3.01 (qd, J = 10.0, 4.4 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.59 (m, 1H), 1.12 – 1.04 (m, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 154.61; MS (ESI), 873.94 $[M - H]^-$.

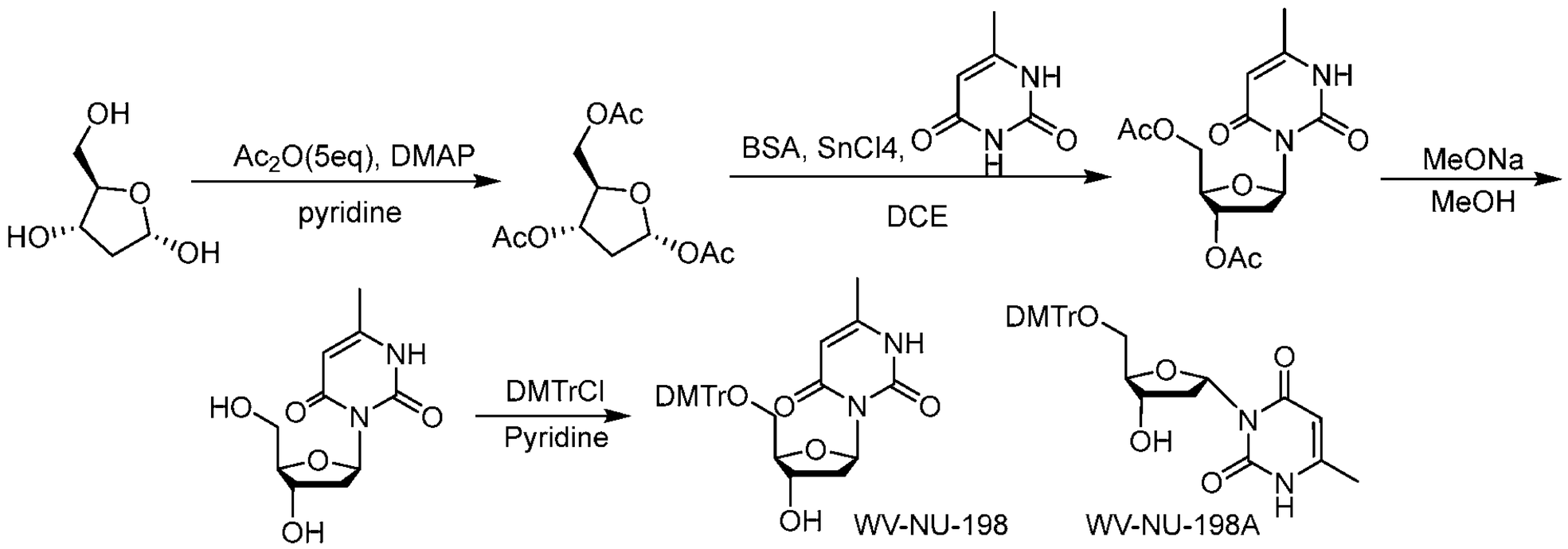
[001294] Synthesis of N-(1-((R)-3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)propyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide



[001295] To a solution of dry N-[1-[(2R)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-hydroxy-propyl]-2-oxo-pyrimidin-4-yl]benzamide (4.81 g, 8.13 mmol) in THF (48 mL) was added triethylamine (6.12 mL, 43.91 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.9*M* in THF, 16.3 mL, 14.64 mmol) was added dropwise. The off-white slurry was stirred at rt for 5 hr. TLC and LCMS showed the reaction was complete. The reaction was quenched by water (146 uL). Anhydrous $MgSO_4$ (1.94 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as a light-brown foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 5% triethylamine) as the gradient. The first half of the fractions of the major peak was still not pure, which was purified again by normal phase column chromatography applying 30-100% DCM in hexanes (each mobile phase contained 2.5% triethylamine) as the gradient. The pure desired product fractions from the two columns were combined and concentrated to afford the title compound as a brownish off-white foam (4.69 g, 65.9%

yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (bs, 1H), 7.96 (dt, J = 7.2, 1.3 Hz, 2H), 7.91 – 7.84 (m, 2H), 7.66 – 7.57 (m, 3H), 7.56 – 7.46 (m, 7H), 7.39 – 7.33 (m, 4H), 7.29 (t, J = 7.7 Hz, 2H), 7.21 (tt, J = 7.4, 1.3 Hz, 1H), 6.87 – 6.81 (m, 4H), 5.08 (q, J = 6.2 Hz, 1H), 4.59 (tdd, J = 12.1, 8.9, 4.1 Hz, 1H), 4.32 (dd, J = 13.4, 3.2 Hz, 1H), 3.791 (s, 3H), 3.789 (s, 3H), 3.78 – 3.73 (m, 1H), 3.58 (dd, J = 13.4, 8.9 Hz, 1H), 3.48 (dd, J = 14.3, 6.4 Hz, 1H), 3.46 – 3.39 (m, 1H), 3.30 (dd, J = 14.2, 6.4 Hz, 1H), 3.23 (dd, J = 10.0, 3.7 Hz, 1H), 3.17 (dd, J = 10.0, 5.4 Hz, 1H), 3.07 – 2.98 (m, 1H), 1.85 – 1.70 (m, 2H), 1.69 – 1.63 (m, 1H), 1.08 (dq, J = 11.7, 9.5 Hz, 1H); ^{31}P NMR (243 MHz, $CDCl_3$) δ 154.17; MS (ESI), 873.94 $[M - H]^-$.

[001296] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-198) and 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-198A)



[001297] **Step 1**. To a solution of (2S,4S,5R)-5-(hydroxymethyl)tetrahydrofuran-2,4-diol (50 g, 372.77 mmol, 1 *eq*) in pyridine (300 mL) was added DMAP (4.55 g, 37.28 mmol, 0.1 *eq*) at 15°C and drop-wise Ac_2O (190.28 g, 1.86 mol, 174.57 mL, 5 *eq*). The mixture was stirred at 15°C for 12 hr. Pyridine was removed rotary evaporators and the residue was co-evaporated with toluene (2*50 mL). The residue was diluted with DCM (300 mL) and washed with 1M HCl (100 mL) and then sat.$NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered and concentrated to get crude product (2R,4S,5R)-5-(acetoxymethyl)tetrahydrofuran-2,4-diyl diacetate (95 g, 365.05 mmol, 97.93% yield) as a white solid.

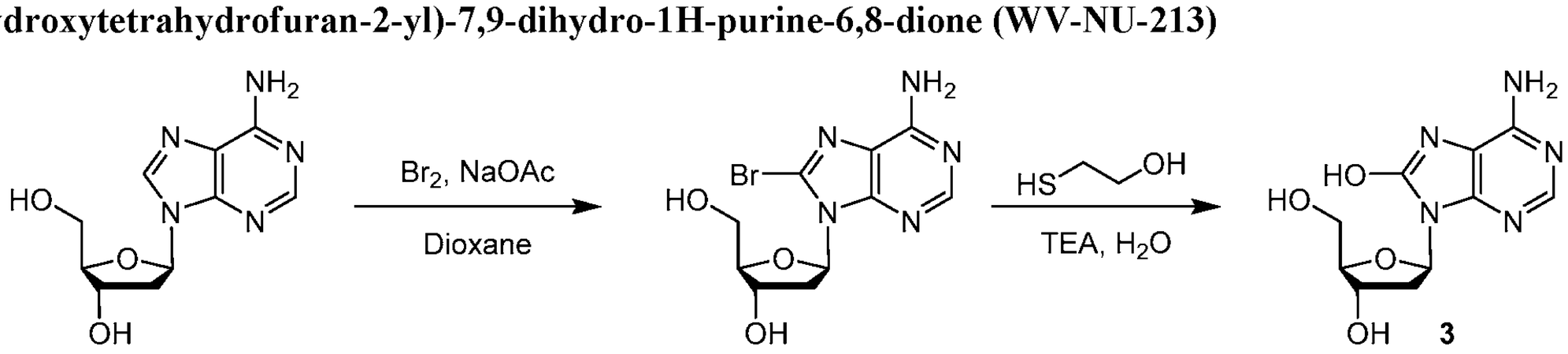
[001298] **Step 2**. To a solution of (2R,4S,5R)-5-(acetoxymethyl)tetrahydrofuran-2,4-diyl diacetate (14.54 g, 115.28 mmol, 1.5 *eq*) kept under argon was dissolved in DCE (300 mL), BSA (46.90 g, 230.56 mmol, 56.99 mL, 3 *eq*) was added, the mixture was stirred at 80°C for 0.5hr until the mixture was clear, and with vigorous stirring, 6-methylpyrimidine-2,4(1H,3H)-dione (20 g, 76.85 mmol, 1 *eq*) in DCE (150 mL) and then $SnCl_4$ (22.02 g, 84.54 mmol, 9.88 mL, 1.1 *eq*) dropwise to a slightly yellowish solution at 0°C. The mixture was stirred at 15°C for 12hr. The reaction mixture was quenched by addition $NaHCO_3$ 20 mL and extracted with DCM 45 mL (15 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give ((2R,3S,5R)-3-acetoxy-5-(4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (20 g, 61.29 mmol, 79.75% yield) as a white solid. LCMS $(M-H)^-$

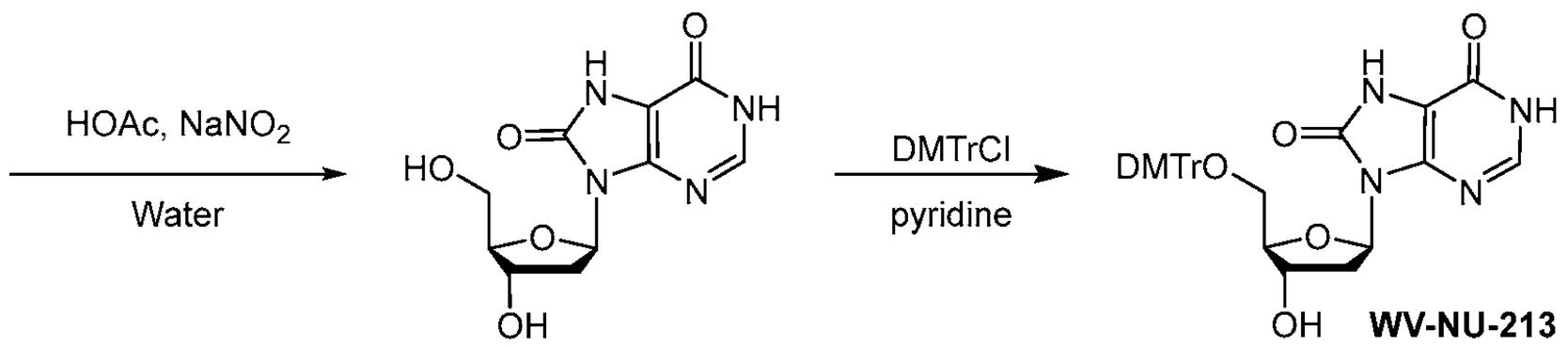
:325.1.

[001299] **Step 3.** To a solution of ((2R,3S,5R)-3-acetoxy-5-(4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (16 g, 49.03 mmol, 1 *eq*) in MeOH (160 mL) was added NaOMe (6.62 g, 122.59 mmol, 2.5 *eq*). The mixture was stirred at 15°C for 3hr. The reaction mixture was quenched by addition NH_4Cl (400cmg), and then concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether： Ethyl acetate=1:0 to 0:1) to give 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (8 g, 33.03 mmol, 88.89% yield) as a white solid. LCMS: ($M-H^+$):241.0.

[001300] **Step 4.** To a solution of 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (4 g, 16.51 mmol, 1 *eq*) in PYRIDINE (90 mL) was added DMTCl (6.71 g, 19.82 mmol, 1.2 *eq*). The mixture was stirred at 15°C for 2hr. The reaction mixture was extracted with DCM (100 mL * 3). The combined organic layers were dried over by Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate=1:0 to 0:1) and repurified by reversed-phase HPLC (column: Phenomenex Titank C18 Bulk 250*70mm 10u; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 46%-66%, 20min @100 mL/min) to give 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-198) (0.83 g, 9.23% yield) as white solid and 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione (WV-NU-198A) (1.65 g, 18.35% yield) as white solid. WV-NU-198: ^{1}HNMR (400 MHz, DMSO-d_6) δ = 11.15 - 10.94 (m, 1H), 7.53 - 7.34 (m, 2H), 7.31 - 7.18 (m, 6H), 6.96 - 6.79 (m, 4H), 6.63 - 6.54 (m, 1H), 5.50 - 5.40 (m, 1H), 5.15 - 5.01 (m, 1H), 4.35 - 4.21 (m, 1H), 3.90 - 3.80 (m, 1H), 3.74 (d, *J* = 1.8 Hz, 6H), 3.40 - 3.29 (m, 1H), 3.27 - 3.12 (m, 1H), 3.10 - 2.96 (m, 1H), 2.14 - 1.89 (m, 4H); LCMS: ($M-H^+$): 543.2. WV-NU-198A: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.10 - 10.89 (m, 1H), 7.59 - 7.43 (m, 2H), 7.42 - 7.29 (m, 6H), 7.26 - 7.17 (m, 1H), 6.95 - 6.81 (m, 4H), 6.14 - 6.02 (m, 1H), 5.81 - 5.71 (m, 1H), 5.39 - 5.31 (m, 1H), 4.92 - 4.76 (m, 1H), 3.79 - 3.68 (m, 6H), 3.65 (br s, 1H), 3.56 - 3.49 (m, 1H), 3.45 - 3.40 (m, 1H), 3.37 - 3.29 (m, 1H), 2.76 (br t, *J* = 11.9 Hz, 1H), 2.67 - 2.59 (m, 1H), 2.07 (s, 1H), 1.99 - 1.92 (m, 3H), 1.55 - 1.40 (m, 1H); LCMS: ($M-H^+$):543.2.

[001301] Synthesis of 9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-7,9-dihydro-1H-purine-6,8-dione (WV-NU-213)





[001302] Step 1. For two batches: To a solution of (2R,3S,5R)-5-(6-amino-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (50 g, 199.01 mmol, 1 *eq.*) in dioxane (400 mL) and AcONa (0.5 M, 1.87 L, 4.71 *eq.*) buffer (pH 4.3) , a solution of Br_2 (38.16 g, 238.81 mmol, 12.31 mL, 1.2 *eq.*) was added dropwise while stirring. The mixture was stirred at 15 °C for 12h. The two batches were combined for work up. To the mixture conc. $Na_2S_2O_5$ was added until the red color vanished. The mixture was neutralized to pH 7.0 with 0.5m NaOH. The residue was evaporated, when a white solid precipitated. The solid was filtered off, washed with cold 1,4-dioxane(50 mL), and dried under high vacuum to get (2R,3S,5R)-5-(6-amino-8-bromo-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (110 g, 333.19 mmol, 83.71% yield) as a yellow solid. ^{1}HNMR (400MHz, DMSO-d6) δ = 8.22 - 7.98 (m, 1H), 7.53 (br s, 2H), 6.29 (dd, J = 6.5, 7.9 Hz, 1H), 5.35 (br d, J = 12.3 Hz, 2H), 4.58 - 4.38 (m, 1H), 3.95 - 3.82 (m, 1H), 3.65 (dd, J = 4.5, 11.9 Hz, 1H), 3.48 (br dd, J = 4.5, 11.7 Hz, 1H), 3.36 (br s, 1H), 3.24 (ddd, J = 6.1, 7.8, 13.4 Hz, 1H), 2.19 (ddd, J = 2.6, 6.4, 13.1 Hz, 1H); LCMS:(M+H+):330.14.

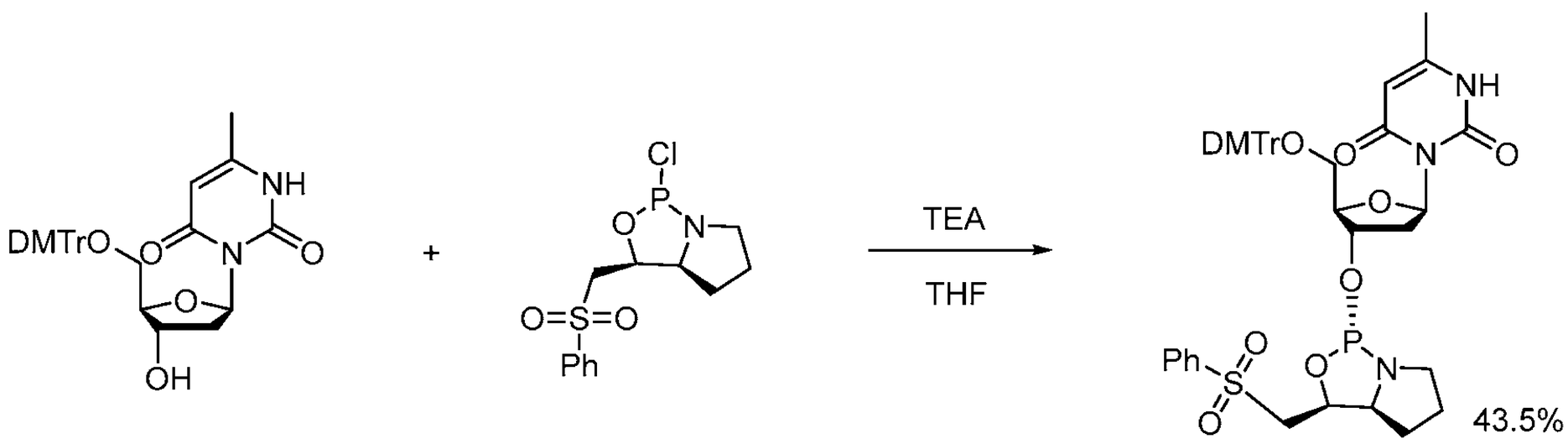
[001303] Step 2. For two batches: A solution of (2R,3S,5R)-5-(6-amino-8-bromo-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (55 g, 166.60 mmol, 1 *eq.*) 2-MERCAPTOETHANOL (39.22 g, 501.90 mmol, 35.01 mL, 3.01 *eq.*) and TEA (168.58 g, 1.67 mol, 231.88 mL, 10 *eq.*) in water (1500 mL) was stirred under 110 °C for 4 hr. The solvent was removed under reduced pressure to give a residue which was purified by MPLC (Dichloromethane: Methanol = 5:1, 10:1) to get 6-amino-9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-8-ol (65 g, 243.23 mmol, 73.00% yield) as a white solid. LCMS :(M+H+):267.24.

[001304] Step 3. A solution of $NaNO_2$ (15.49 g, 224.52 mmol, 2 *eq.*) in Water (60 mL) was added to a stirred solution of 6-amino-9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-8-ol (30 g, 112.26 mmol, 1 *eq.*) in HOAc (1500 mL, 95% purity). The reaction mixture was stirred at 15 °C for 12 hr. The solvent was removed under reduced pressure. The crude product was triturated with DCM (500 ml) at 15 °C for 5 min to give 9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7,9-dihydro-1H-purine-6,8-dione (22 g, 82.02 mmol, 73.06% yield) was obtained as a white solid. ^{1}HNMR (400MHz, DMSO-d_6) δ = 7.98 (s, 1H), 6.12 (t, *J* = 7.3 Hz, 1H), 4.36 (td, *J* = 2.8, 5.8 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.58 (dd, *J* = 5.0, 11.6 Hz, 1H), 3.44 (dd, *J* = 5.3, 11.6 Hz, 1H), 2.96 (ddd, *J* = 6.2, 7.6, 13.3 Hz, 1H), 2.01 (ddd, *J* = 2.8, 6.7, 13.0 Hz, 1H), 1.90 (s, 1H); LCMS:(M+H+):268.23.

[001305] Step 4. To a solution of 9-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7,9-dihydro-1H-purine-6,8-dione (22 g, 82.02 mmol, 1 *eq.*) in PYRIDINE (400 mL) was added DMTCl (22.23 g, 65.62 mmol, 0.8 *eq.*). The mixture was stirred at 15 °C for 12 hr. The reaction mixture was quenched by

addition water 400 mL at 15 °C, and then diluted with water 200 mL and extracted with ethyl acetate 900 mL (300 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 1:0 to 0:1). The crude product was triturated with DCM (300 ml) at 15 °C for 5 min to give WV-NU-213 (13.67 g, 30% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.37 (s, 1H), 7.78 (s, 1H), 7.35 (d, *J* = 7.4 Hz, 2H), 7.26 - 7.14 (m, 7H), 6.80 (dd, *J* = 8.9, 14.5 Hz, 4H), 6.13 (t, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 4.8 Hz, 1H), 4.48 - 4.39 (m, 1H), 3.89 (td, *J* = 4.4, 6.4 Hz, 1H), 3.72 (d, *J* = 3.6 Hz, 6H), 3.33 (s, 1H), 3.20 - 3.03 (m, 2H), 2.96 (td, *J* = 6.5, 12.9 Hz, 1H), 2.15 - 2.05 (m, 1H); LCMS :(M+H-):570.59, LCMS purity: 97.33%.

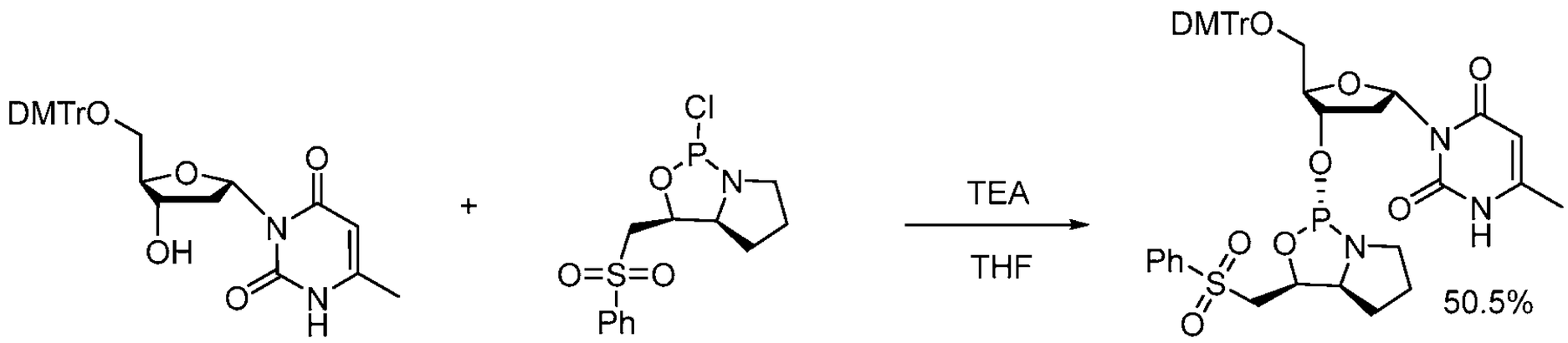
[001306] Synthesis of 3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione



[001307] To a solution of dry 3-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-6-methyl-1H-pyrimidine-2,4-dione (0.83 g, 1.52 mmol) in THF (6.5 mL) was added triethylamine (0.47 mL, 3.35 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.43*M* in THF, 5.32 mL, 2.29 mmol) was added fast dropwise. The resulting cloudy reaction solution was stirred at rt for 5 h. TLC showed the reaction was complete. The reaction was quenched by water (14 μL). Anhydrous $MgSO_4$ (183 mg) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (0.549 g, 43.5% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 9.50 (s, 1H), 7.89 – 7.84 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.32 (ddd, J = 9.2, 5.6, 2.8 Hz, 4H), 7.22 (t, J = 7.6 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 6.79 – 6.73 (m, 4H), 6.71 (dd, J = 8.9, 4.3 Hz, 1H), 5.46 (s, 1H), 4.93 (q, J = 6.1 Hz, 1H), 4.84 (dq, J = 8.8, 6.2 Hz, 1H), 3.92 (td, J = 6.4, 3.9 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.63 (dq, J = 11.8, 5.9 Hz, 1H), 3.43 – 3.27 (m, 5H), 2.94 (qd, J = 10.0, 4.1 Hz, 1H), 2.80 (ddd, J = 13.0, 8.2, 4.3 Hz, 1H), 2.26 (ddd, J = 13.6, 9.0, 6.1 Hz, 1H), 1.99 (s, 3H), 1.83 (dtt, J = 11.9, 7.8, 3.2 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.66 – 1.58 (m, 1H), 1.11 – 1.04 (m, 1H); ^{31}P NMR (243 MHz, Chloroform-d) δ 149.82; MS (ESI), 826.14 $[M - H]^-$.

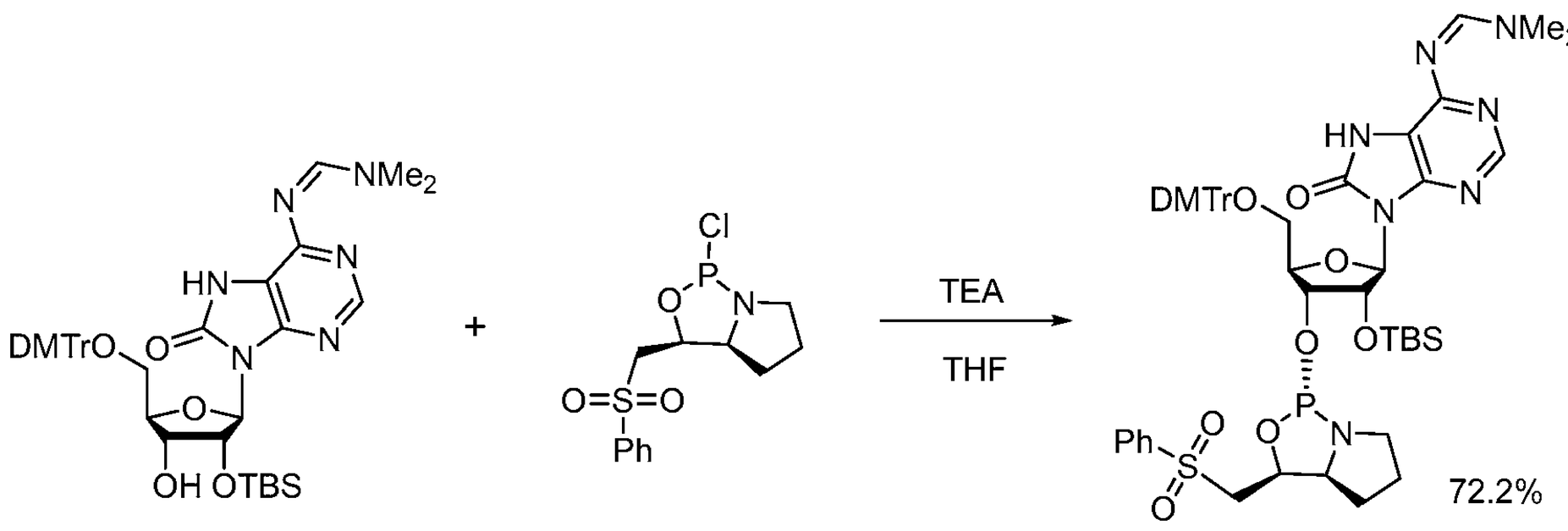
[001308] Synthesis of 3-((2S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-

(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-6-methylpyrimidine-2,4(1H,3H)-dione



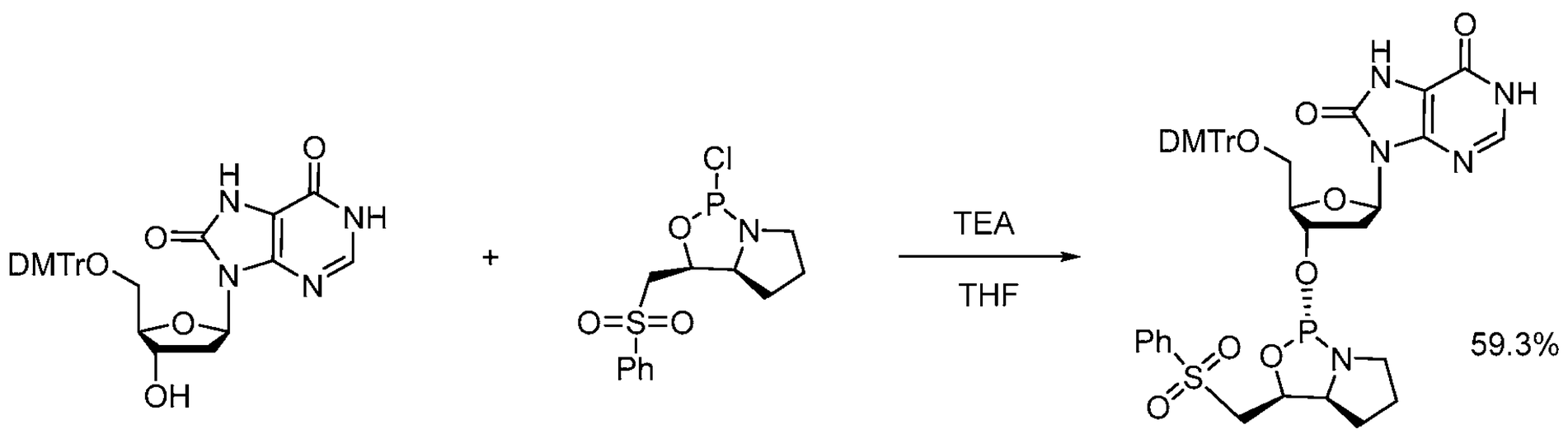
[001309] To a solution of dry 3-[(2S,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-6-methyl-1H-pyrimidine-2,4-dione (1.65 g, 3.03 mmol) in THF (12.5 mL) was added triethylamine (0.93 mL, 6.67 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.43*M* in THF, 10.6 mL, 4.54 mmol) was added fast dropwise. The resulting cloudy reaction solution was stirred at rt for 5 hr. TLC showed the reaction was complete. The reaction was quenched by water (27 μL). Anhydrous $MgSO_4$ (363 mg) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (1.266 g, 50.5% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 9.07 (s, 1H), 7.93 (dd, J = 7.8, 1.6 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.53 (t, J = 7.7 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.41 – 7.36 (m, 4H), 7.25 (d, J = 7.6 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 6.79 (dd, J = 9.0, 2.2 Hz, 4H), 6.16 (d, J = 11.2 Hz, 1H), 5.45 (s, 1H), 5.04 (q, J = 6.0 Hz, 1H), 4.17 – 4.11 (m, 1H), 3.783 (s, 3H), 3.777 (s, 3H), 3.73 – 3.62 (m, 3H), 3.58 – 3.53 (m, 1H), 3.52 – 3.47 (m, 1H), 3.42 (dd, J = 14.6, 5.4 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.95 – 2.88 (m, 1H), 2.86 (dd, J = 10.3, 4.2 Hz, 1H), 2.03 (s, 3H), 1.85 (dp, J = 12.2, 4.5 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.66 (ddt, J = 7.8, 5.5, 2.5 Hz, 1H), 1.61 (dt, J = 13.6, 3.1 Hz, 1H), 1.21 – 1.11 (m, 1H); ^{31}P NMR (243 MHz, Chloroform-d) δ 148.85; MS (ESI), 826.14 $[M - H]^-$.

[001310] Synthesis of (Z)-N'-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-8-oxo-8,9-dihydro-7H-purin-6-yl)-N,N-dimethylformimidamide



[001311] To a solution of dry N'-[9-[(2R,3S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-3-[tert-butyl(dimethyl)silyl]oxy-4-hydroxy-tetrahydrofuran-2-yl]-8-oxo-7H-purin-6-yl]-N,N-dimethyl-formamidine (18.0 g, 23.84 mmol) in THF (135 mL) was added triethylamine (7.31 mL, 52.45 mmol). The reaction flask was set in a water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.43*M* in THF, 83.17 mL, 35.76 mmol) was added fast dropwise. The water bath was removed. The cloudy reaction solution was stirred at rt for 3 hr. TLC and LCMS showed the reaction was incomplete. Additional TEA (1.46 mL, 10.47 mmol) was added. Additional (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.43*M* in THF, 16.6 mL, 7.14 mmol) was also added fast dropwise. Stirred for another 1 hr. TLC showed the reaction was complete. The reaction was quenched by water (343 μL). Anhydrous $MgSO_4$ (4.577 g) was added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as a white foam. The crude product was purified by normal phase column chromatography applying 20-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (17.87 g, 72.2% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 7.87 – 7.83 (m, 2H), 7.56 – 7.52 (m, 1H), 7.49 – 7.42 (m, 4H), 7.38 – 7.31 (m, 4H), 7.20 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.17 – 7.12 (m, 1H), 6.78 – 6.72 (m, 4H), 5.94 (d, *J* = 5.5 Hz, 1H), 5.34 (t, *J* = 5.4 Hz, 1H), 4.96 (q, *J* = 6.2 Hz, 1H), 4.78 (dt, *J* = 10.8, 4.5 Hz, 1H), 4.01 (q, *J* = 4.4 Hz, 1H), 3.75 (s, 6H), 3.67 (dq, *J* = 11.5, 6.0 Hz, 1H), 3.48 – 3.35 (m, 4H), 3.17 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.13 (s, 3H), 3.10 (s, 3H), 3.03 (qd, *J* = 9.5, 4.0 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.78 – 1.72 (m, 1H), 1.69 – 1.62 (m, 1H), 1.15 – 1.06 (m, 1H), 0.81 (s, 9H), -0.02 (s, 3H), -0.14 (s, 3H); ^{31}P NMR (243 MHz, Chloroform-d) δ 152.36; MS (ESI), 1036.85 $[M - H]^-$.

[001312] Synthesis of 9-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)-7,9-dihydro-1H-purine-6,8-dione

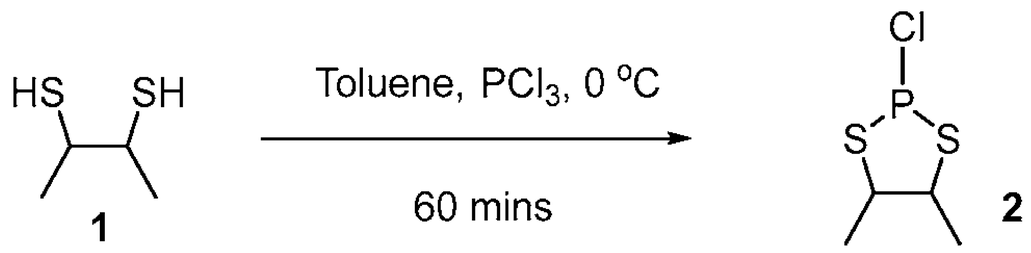


[001313] To a solution of dry 9-[(2R,4R,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hydroxy-tetrahydrofuran-2-yl]-1,7-dihydropurine-6,8-dione (6.0 g, 10.52 mmol) in THF (90 mL) was added triethylamine (3.08 mL, 22.08 mmol). (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.89*M* in THF, 18.9 mL, 16.82 mmol) was added fast dropwise. Stirred at rt for 2 hr. LCMS showed the conversion rate was around 67%. Stirred for another 6 hr. TLC showed the starting material was faint. The reaction was quenched by water (113 μL). Anhydrous $MgSO_4$ (1.51 g) was

added. The mixture was filtered through celite, and the filtrate was concentrated to afford the crude product as an off-white foam. The crude product was purified by normal phase column chromatography applying 0-100% ACN in EtOAc (each mobile phase contained 5% triethylamine) as the gradient to afford the title compound as an off-white foam (5.32 g, 59.3% yield). ^{1}H NMR (600 MHz, DMSO-d6) δ 11.42 (s, 2H), 7.88 – 7.81 (m, 3H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.25 – 7.14 (m, 7H), 6.79 (dd, J = 18.2, 8.5 Hz, 4H), 6.11 (dd, J = 8.1, 4.6 Hz, 1H), 5.10 – 5.00 (m, 2H), 3.86 – 3.79 (m, 2H), 3.73 – 3.69 (m, 6H), 3.69 – 3.65 (m, 1H), 3.58 (dt, J = 9.6, 5.3 Hz, 1H), 3.24 (dd, J = 14.3, 7.6 Hz, 1H), 3.11 (dd, J = 10.4, 3.8 Hz, 1H), 3.08 – 3.03 (m, 1H), 2.85 (dt, J = 13.2, 6.1 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.60 (qd, J = 9.8, 3.9 Hz, 1H), 2.27 (dt, J = 14.1, 7.4 Hz, 1H), 1.63 – 1.50 (m, 2H), 1.11 (q, J = 10.2, 9.7 Hz, 1H); ^{31}P NMR (243 MHz, DMSO-d6) δ 144.02; MS (ESI), 852.62 [M - H]$^{-}$.

[001314] Preparation for additional compounds useful for oligonucleotide preparation were described below as examples.

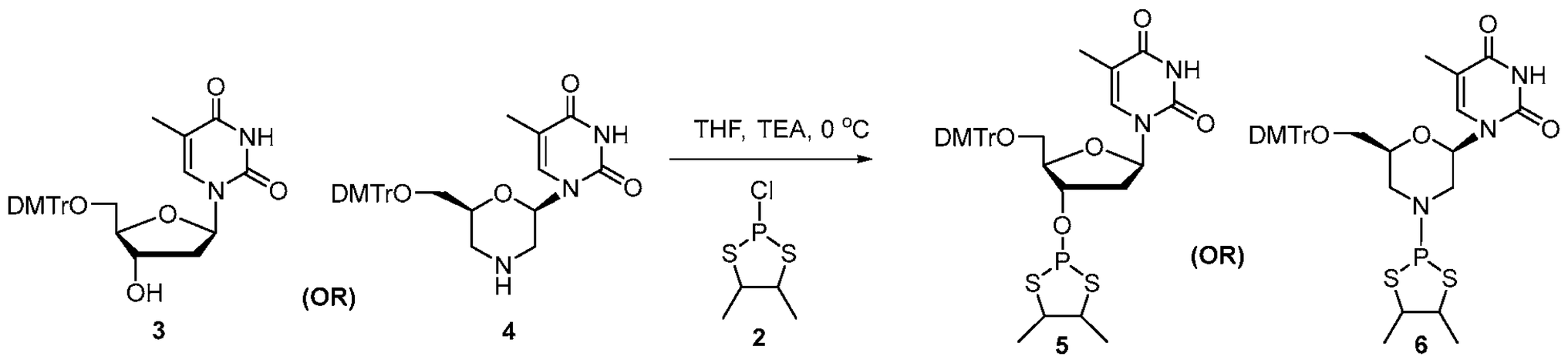
[001315] General experimental procedure (A) for chloro reagent (2)



[001316] Dithiol (360 mmol) was dissolved in toluene (720 mL) under argon (3000 mL single neck flask) then 4-methylmorpholine (35.4 mL, 792 mmol) was added. This mixture was added dropwise via cannula over 30 min to an ice-cold solution of phosphorus trichloride (720 mL, 396 mmol) in toluene (720 mL) under argon atmosphere. After warming to room temperature for 1 h, the mixture was filtered carefully under vacuum/argon. The resulting filtrate was concentrated by rotary evaporation (flushing with Ar) then dried under high vacuum for 2 h. The resulting crude compound was isolated as thick oil, which was dissolved in THF to obtain a 1 M stock solution and this solution was used in the next step without further purification.

[001317] Data for 2: Synthesized from compound 1, by following the general procedure A. ^{31}P NMR (243 MHz, THF-$CDCl_3$, 1:2) δ 168.77, 161.4

[001318] General experimental procedure (B) for monomers (5 and 6)



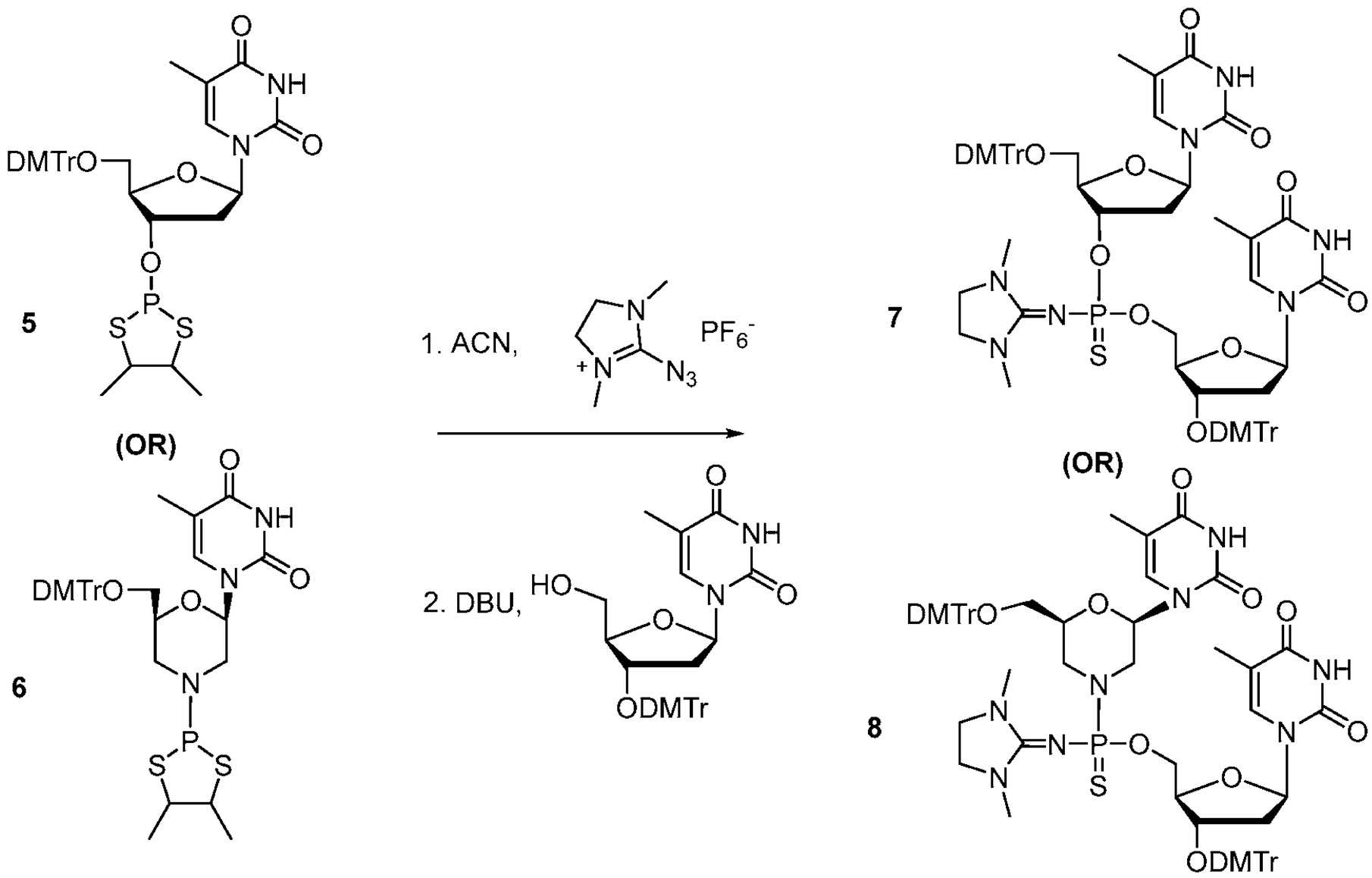
[001319] The 5'-ODMTr protected nucleoside 3 or 4 (6.9 mmol) was dried in a three neck 250 mL round bottom flask by co-evaporating with anhydrous toluene (50 mL) followed by under high vacuum for 18 h. The dried nucleoside was dissolved in dry THF (35 mL) under argon atmosphere. Then, triethylamine (24.4 mmol, 3.5 equiv.) was added into the reaction mixture, then cooled to ~ - 10 °C. A THF solution of the crude chloro

reagent (1 M solution, 2.5 equiv., 17.4 mmol) was added to the above mixture through cannula over ~5 min, then, gradually warmed to room temperature over about 1 h. LCMS showed that the starting material was consumed. The reaction mixture was filtered carefully under vacuum/argon and the resulting filtrate was concentrated under reduced pressure to give a yellow foam which was further dried under high vacuum overnight. Crude mixture was purified by silica gel column [Column was pre-deactivated using acetonitrile then ethyl acetate (5% TEA) and then equilibrated using ethyl acetate-hexanes] chromatography using ethyl acetate and hexane as eluents.

[001320] Stereorandom (Rp/Sp) monomer 5: Yield 86%. Reaction was carried out using nucleoside 3 and chloro reagent 2 by following the general procedure B. ^{31}P NMR (243 MHz, $CDCl_3$) δ 171.62, 155.50, 146.84, 146.17; MS (ES) *m/z* calculated for $C_{35}H_{39}N_2O_7PS_2$ $[M+K]^+$ 733.16, Observed: 733.40 $[M + K]^+$.

[001321] Stereorandom (Rp/Sp) monomer 6: Yield 73%. Reaction was carried out using nucleoside 4 and chloro reagent 2 by following the general procedure B. ^{31}P NMR (243 MHz, $CDCl_3$) δ 121.87, 106.20, 93.58, 92.99; MS (ES) *m/z* calculated for $C_{35}H_{40}N_3O_6PS_2$ $[M+K]^+$ 773.28, Observed: 773.70 $[M + K]^+$.

[001322] General experimental procedure (C) for PS-PN dimers (7 and 8):



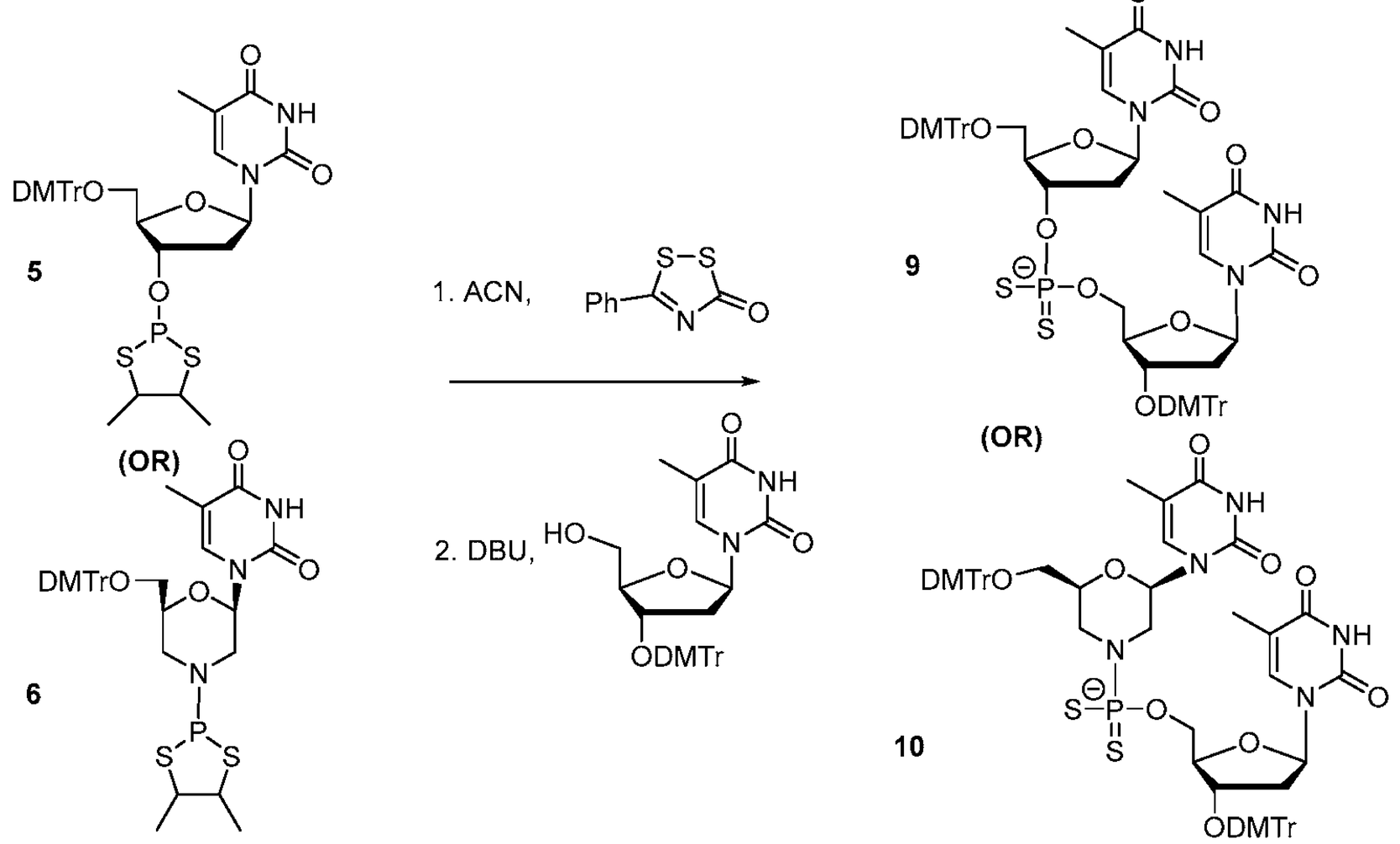
[001323] To a stirred solution of monomer 5 or 6 (0.10 mmol, 2 equiv., pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (0.5 mL) was added a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (0.11 mmol, 2.25 equiv.) in acetonitrile (0.2 mL) under argon atmosphere at room temperature. Resulting reaction mixture was stirred for 10 mins then DMTr protected alcohol (0.05 mmol, pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (0.25 mL) and 1,8-Diazabicyclo [5.4.0] undec-7-ene (0.23 mmol, 5 equ, 0.23 ml of 1 M solution in dry acetonitrile) are added. The reaction was monitored and analyzed by LCMS.

Approximate reaction completion time 10-20 mins.

[001324] Stereorandom dimer 7: Reaction was carried out using 5 by following the general procedure C. MS (ES) *m/z* calculated for $C_{67}H_{72}N_7O_{14}PS$ $[M+K]^+$ 1300.42, Observed: 1300.70 $[M + K]^+$.

[001325] Stereopure (Rp) dimer 8: Reaction was carried out using 6 by following the general procedure C. MS (ES) *m/z* calculated for $C_{67}H_{73}N_8O_{13}PS$ $[M+K]^+$ 1299.44, Observed: 1299.65 $[M + K]^+$.

[001326] General experimental procedure (D) for PS-PS dimers (9 and 10):

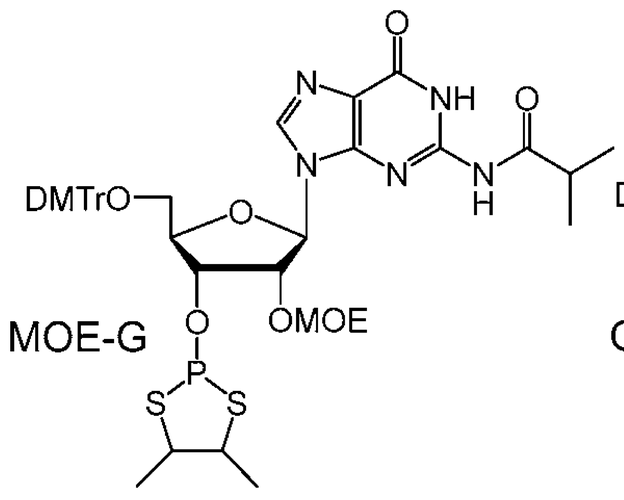


[001327] To a stirred solution of monomer 5 or 6 (0.10 mmol, 2 equiv., pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (0.5 mL) was added a solution of 5-phenyl-3H-1,2,4-dithiazol-3-one (0.12 mmol, 2.5 equiv., 0.2 M) in acetonitrile under argon atmosphere at room temperature. Resulting reaction mixture was stirred for 10 mins then DMTr protected alcohol (0.05 mmol, 1 equ, pre-dried by co-evaporation with dry acetonitrile and kept it under vacuum for minimum 12 h) in dry acetonitrile (0.2 mL) and 1,8-Diazabicyclo [5.4.0] undec-7-ene (0.23 mmol, 5 equ, 1 M solution in dry acetonitrile) are added. Once the reaction was completed (monitored by LCMS) then the reaction mixture was analyzed by LCMS.

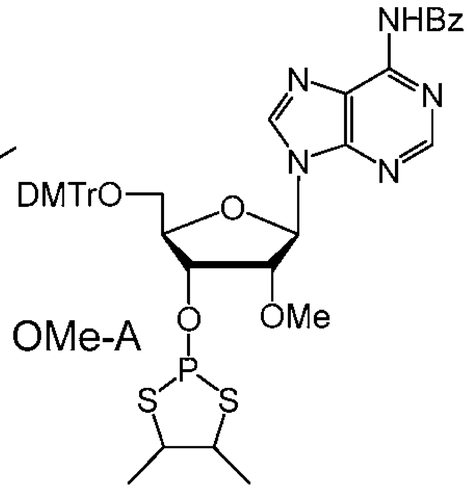
[001328] Dimer 9: Reaction was carried out using monomer 5 by following the general procedure D. Reaction completion time about 30 mins. MS (ES) *m/z* calculated for $C_{62}H_{62}N_4O_{14}PS_2$ $[M]^-$ 1181.34, Observed: 1181.66 $[M]^-$.

[001329] Dimer 10: Reaction was carried out using monomer 6 by following the general procedure D. Reaction completion time about 20 h. MS (ES) *m/z* calculated for $C_{62}H_{63}N_5O_{13}PS_2$ $[M]^-$ 1180.36, Observed: 1180.71 $[M]^-$.

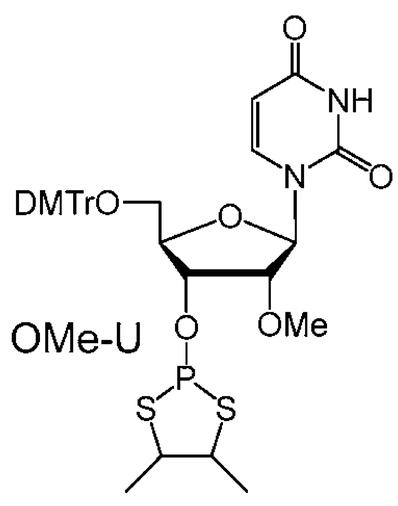
[001330] Additional useful compounds were prepared as examples:



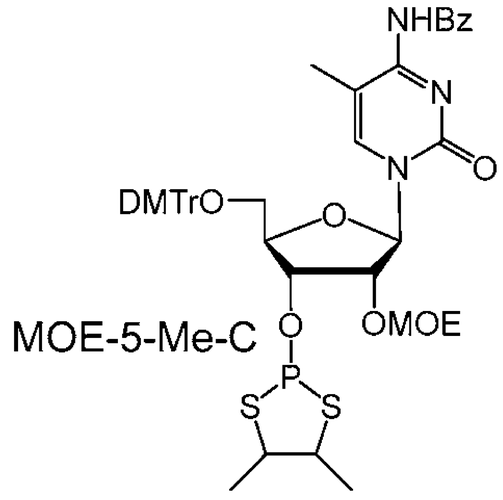
451



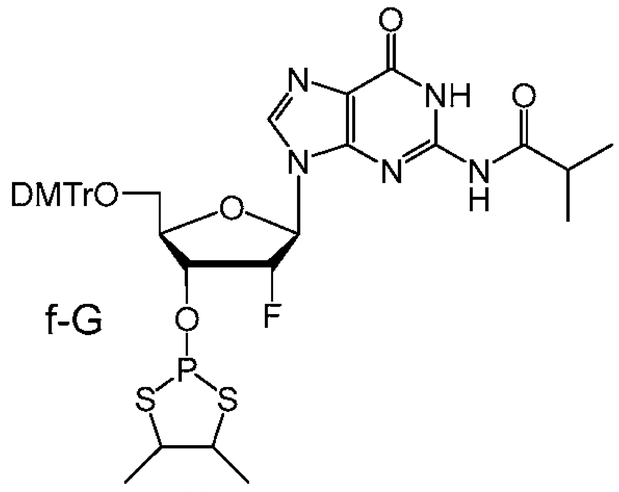
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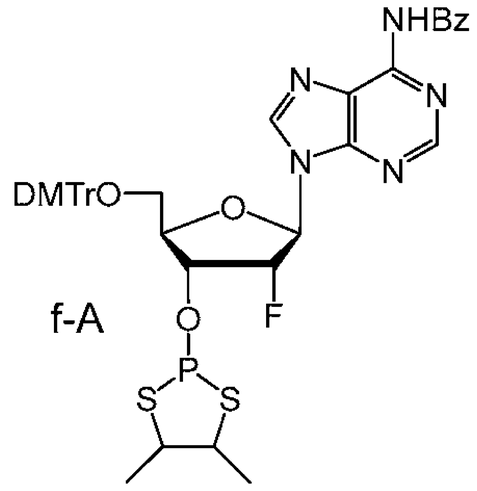
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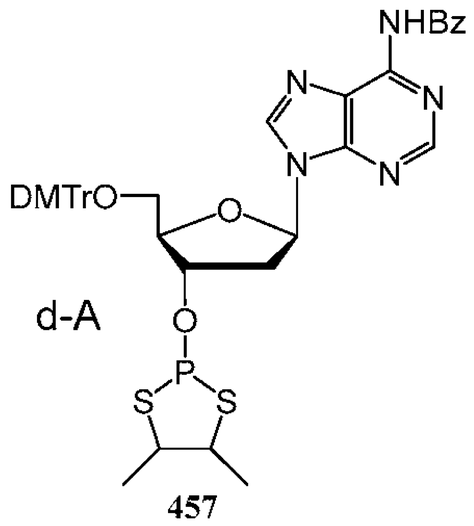
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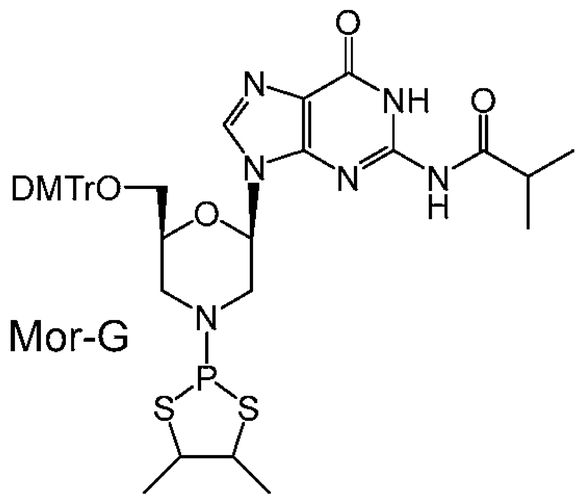
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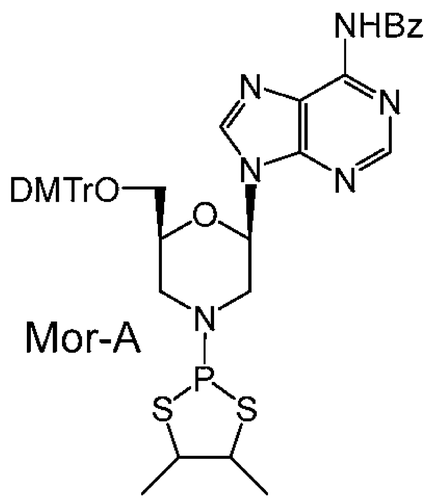
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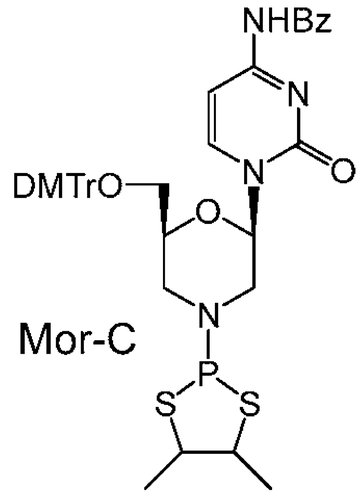
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460

[001331] MOE-G monomer 451: Yield 81%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 175.14, 158.52, 150.30, 148.81; MS (ES) *m/z* calculated for $C_{42}H_{50}N_5O_9PS_2$ $[M+H]^+$ 864.29, Observed: 864.56 $[M + H]^+$.

[001332] OMe-A monomer 452: Yield 92%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 175.65, 159.27, 151.04, 150.10; MS (ES) *m/z* calculated for $C_{43}H_{44}N_5O_7PS_2$ $[M+H]^+$ 838.25, Observed: 838.05 $[M + H]^+$.

[001333] OMe-U monomer 453: Yield 94%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 175.09, 162.04, 154.12, 153.58; MS (ES) *m/z* calculated for $C_{35}H_{39}N_2O_8PS_2$ $[M+K]^+$ 749.15, Observed: 749.06 $[M + K]^+$.

[001334] MOE-5-Me-C monomer 454: Yield 91%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 175.53, 162.04, 153.78, 153.61; MS (ES) *m/z* calculated for $C_{45}H_{50}N_3O_9PS_2$ $[M+H]^+$ 872.28, Observed: 872.16 $[M + H]^+$.

[001335] f-G monomer 455: Yield 97%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 176.88 (d), 161.94 (d), 154.16 (d), 152.48 (d); MS (ES) *m/z* calculated for $C_{39}H_{43}FN_5O_7PS_2$ $[M+H]^+$ 808.24, Observed: 808.65 $[M + H]^+$.

[001336] f-A monomer 456: Yield 99%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 177.43 (d), 159.63 (d), 149.76 (d), 149.55 (d); MS (ES) *m/z* calculated for $C_{42}H_{41}FN_5O_6PS_2$ $[M+H]^+$ 826.23, Observed: 826.56 $[M + H]^+$.

[001337] dA monomer 457: Yield 98%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 171.85, 154.47, 146.19, 144.48; MS (ES) *m/z* calculated for $C_{42}H_{42}N_5O_6PS_2$ $[M+K]^+$ 846.20, Observed: 846.56 $[M + K]^+$.

[001338] Mor-G monomer 458: Yield 72%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 121.26, 105.98, 93.48, 93.24;

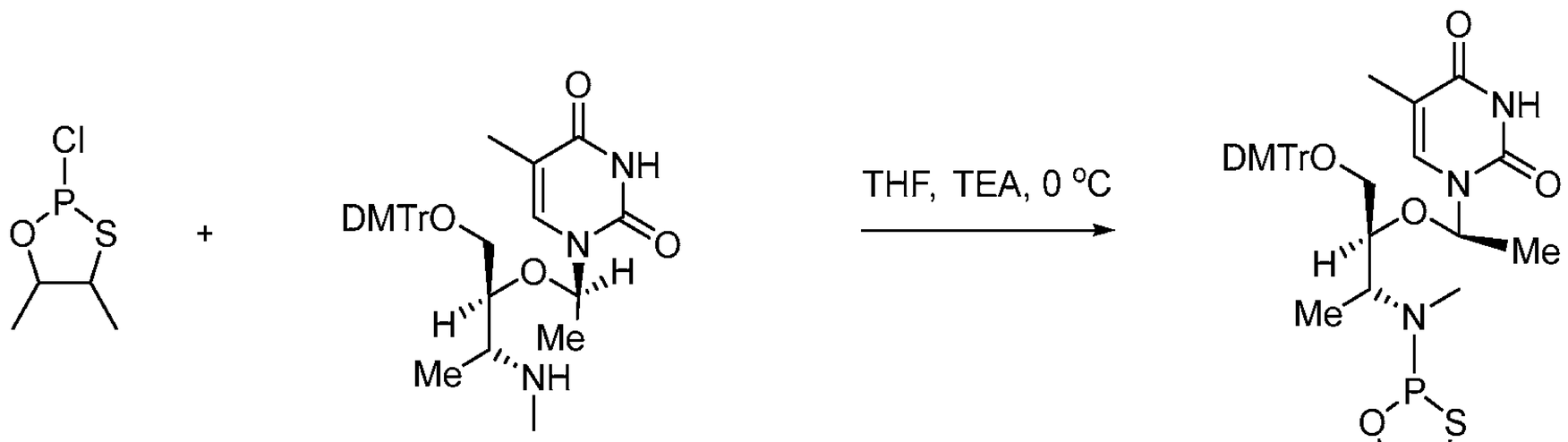
MS (ES) *m/z* calculated for $C_{39}H_{45}N_6O_6PS_2[M+K]^+$ 827.22, Observed: 827.60 $[M + K]^+$.

[001339] Mor-A monomer 459: Yield 37%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 121.87, 106.17, 93.23, 93.05; MS (ES) *m/z* calculated for $C_{42}H_{43}N_6O_5PS_2$ $[M+K]^+$ 845.21, Observed: 845.32 $[M + K]^+$.

[001340] Mor-C monomer 460: Yield 68%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 122.34, 106.05, 93.33, 92.6116; MS (ES) *m/z* calculated for $C_{41}H_{43}N_4O_6PS_2$ $[M+K]^+$ 821.20, Observed: 821.54 $[M + K]^+$.

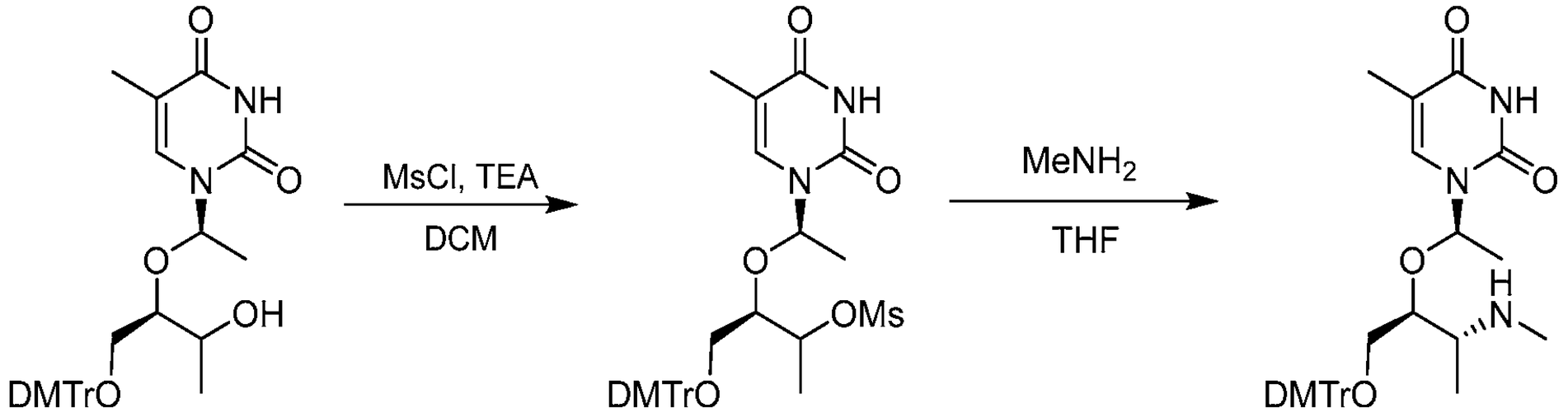
[001341] In some embodiments, a sugar is acyclic. In some embodiments, the present disclosure provides technolgoies, e.g., reagents (e.g., phosphoramidites), conditions, methods, etc. for prepare oligonucleotides comprising a cyclic sugars. An example is described below for sm18.

[001342] Certain acyclic morpholine monomers.



WV-SM-56A **801**

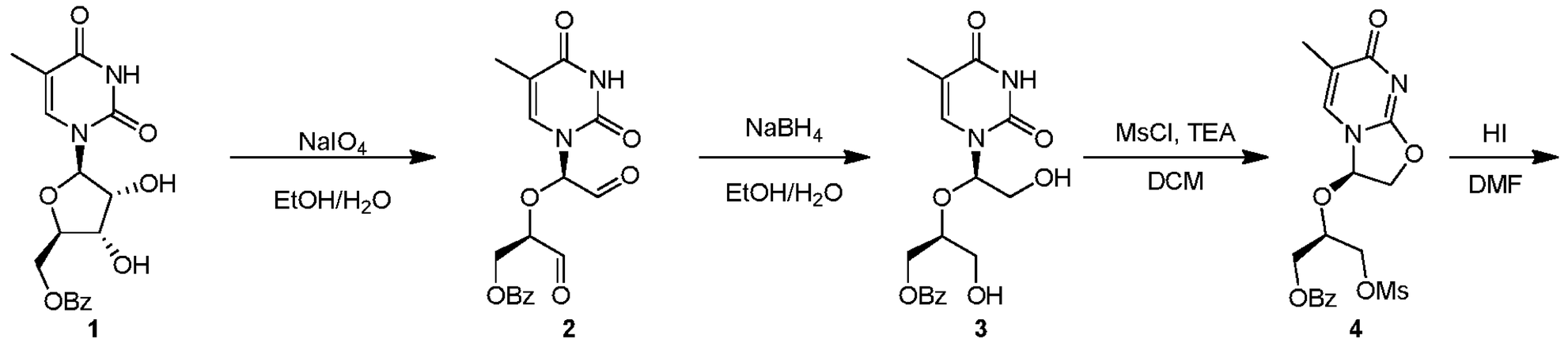
[001343] A 5'-ODMTr protected morpholino nucleoside (5.05 mmol) was dried in a three neck 100 mL round bottom flask by co-evaporating with anhydrous toluene (50 mL) followed by under high vacuum for 18 h. The dried nucleoside was dissolved in dry THF (25 mL) under argon atmosphere. Then, triethylamine (17.6 mmol, 3.5 equiv.) was added into the reaction mixture, then cooled to ~ - 10 °C. A THF solution of the crude chloro reagent (1.4 M solution, 1.8 equiv., 9.09 mmol) was added to the above mixture through cannula over ~3 min, then, gradually warmed to room temperature over about 1 h. LCMS showed that the starting material was consumed. Then filtered carefully under vacuum/argon and the resulting filtrate was concentrated under reduced pressure to give a yellow foam which was further dried under high vacuum overnight. Crude mixture was purified by silica gel column [Column was pre-deactivated using acetonitrile then ethyl acetate (5% TEA) and then equilibrated using ethyl acetate-hexanes] chromatography using ethyl acetate and hexane as eluents. Yield 66%. ^{31}P NMR (243 MHz, $CDCl_3$) δ 154.93, 154.65, 154.58, 154.23, 150.54, 150.17, 145.69, 145.26; MS (ES) *m/z* calculated for $C_{37}H_{46}N_3O_7PS$ $[M+K]^+$ 746.24, Observed: 746.38 $[M + K]^+$.

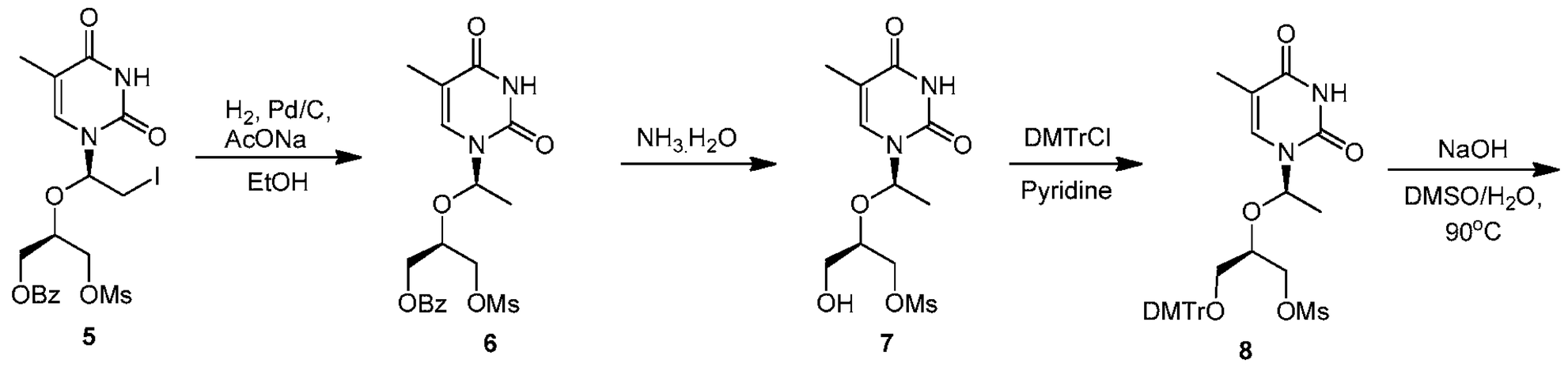


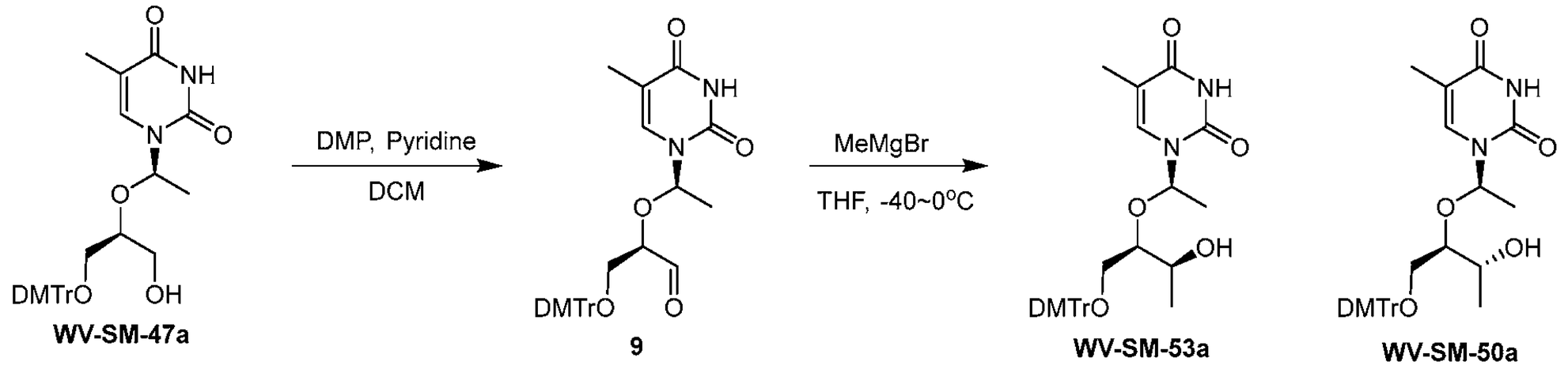
WV-SM-53a/50a 27 WV-SM-56a

[001344] To a solution of WV-SM-53a/50a (6 g, 10.70 mmol) in DCM (40 mL) was added Et_3N (3.25 g, 32.11 mmol) and MsCl (2.45 g, 21.40 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred at 0 °C for 4 hr. TLC showed WV-SM-53a/50a was consumed and one new spot was detected. The reaction mixture was quenched by addition sat. $NaHCO_3$ (aq., 50 mL), and then extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 27 (8.0 g, crude) was obtained as a brown oil. TLC Petroleum ether: Ethyl acetate = 1:3, R_f = 0.50.

[001345] Two batches: To a solution of compound 27 (3.42 g, 5.35 mmol,) in THF (20 mL) was added methanamine (10 g, 96.60 mmol, 30% purity). The mixture was stirred at 100 °C for 160 hr. LC-MS showed compound 27 was consumed and one main peak with desired MS was detected. TLC showed one main spot. 2 batches were combined and the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO_2, Petroleum ether/Ethyl acetate = 5:1 to 0:1, 5% TEA). WV-SM-56a (2.9 g, 47.21% yield) was obtained as yellow solid. ^1H NMR (400MHz, CHLOROFORM-d) δ = 7.29 - 7.24 (m, 2H), 7.20 - 7.06 (m, 8H), 6.72 (d, J=8.8 Hz, 4H), 6.08 - 5.87 (m, 1H), 3.71 (s, 6H), 3.58 - 3.42 (m, 1H), 3.19 - 3.05 (m, 1H), 3.05 - 2.91 (m, 1H), 2.83 - 2.75 (m, 1H), 2.72 (d, J=4.8 Hz, 2H), 2.31 (s, 3H), 1.61 (dd, J=0.9, 5.9 Hz, 3H), 1.36 (d, J=5.9 Hz, 3H), 0.96 - 0.77 (m, 3H). ^{13}C NMR (101MHz, CHLOROFORM-d) δ = 163.71, 163.62, 158.47, 150.74, 150.58, 144.72, 135.94, 135.89, 135.86, 135.25, 135.15, 130.02, 129.93, 129.89, 127.90 (dd, J=2.9, 22.0 Hz, 1C), 126.83, 126.81, 113.10, 113.08, 111.28, 111.24, 86.45, 86.39, 81.89, 81.82, 81.00, 80.58, 63.39, 63.15, 60.40, 56.02, 55.23, 34.52, 34.17, 26.41, 23.11, 21.66, 21.59, 15.57, 15.09, 14.20, 12.46, 12.41. HPLC purity: 90.87%. LCMS ($M+Na^+$): 596.3. SFC: dr = 52.46: 47.54. TLC (ethyl acetate: methanol = 9:1), R_f = 0.19.







[001346] Preparation of Compound 2. 2 batches: To a solution of compound 1 (50 g, 137.99 mmol) in EtOH (1000 mL) was added $NaIO_4$ (30.00 g, 140.26 mmol) in H_2O (500 mL). The mixture was stirred in dark at 15 °C for 2 hr. TLC indicated compound 1 was consumed and one new spot formed. Compound 2 (99.44 g, crude) was obtained as a white suspension liquid, which was used next step. TLC (Ethyl acetate: Methanol = 9:1), $R_f = 0.49$.

[001347] Preparation of Compound 3. 2 batches: To a stirred solution of compound 2 (49.72 g, 137.99 mmol) in EtOH (1000 mL) and H_2O (500 mL) was added $NaBH_4$ (10.44 g, 275.98 mmol) in small portions at 0 °C. The mixture was stirred at 15 °C for 1 hr. TLC indicated compound 2 was consumed and one new spot formed. 1N HCl was added to pH = 7. The solvent was removed to yield a brown solid. The solid was added sat. Na_2SO_3 (aq., 500 mL) and then extracted with EtOAc (500 mL*8). The combined organic phase was dried by Na_2SO_4. Removal of the solvent under reduced pressure gave the product. Compound 3 (86.7 g, 86.22% yield) was obtained as a white solid. LCMS ($M+Na^+$) 386.9, purity 96.31%. TLC (Ethyl acetate: Methanol = 9:1), $R_f = 0.38$.

[001348] Preparation of compound 4. To a solution of compound 3 (86.7 g, 237.96 mmol) and TEA (120.40 g, 1.19 mol) in DCM (700 mL) was added MsCl (59.97 g, 523.51 mmol) in DCM (300 mL). The mixture was stirred at 0 °C for 4 hr. TLC indicated compound 3 was consumed, and two new spots formed. The reaction mixture was quenched by addition water (500 mL) and stayed for 36 hr. TLC indicated the intermediate was consumed, and one spot left. The water layer was extracted with DCM (800 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 0:1 and then MeOH/EtOAc = 0/1 to 1/10). Compound 4 (75 g, 74.26% yield) was obtained as a white solid. TLC (Petroleum ether: Ethyl acetate = 0: 1), $R_f = 0.38$; (Ethyl acetate: Methanol = 9: 1), $R_f = 0.13$.

[001349] Preparation of compound 5. To a solution of compound 4 (75 g, 176.71 mmol) in DMF (650 mL)

was added HI (100.46 g, 353.42 mmol, 59.09 mL, 45% purity). The mixture was stirred at 15 °C for 0.5 hr. TLC showed compound 4 was consumed and one main spot was detected. The reaction mixture was quenched by sat. $NaHCO_3$ (aq.) to pH = 7. The residue was extracted with EtOAc (800 mL * 5). The combined organic layers were washed with brine (600 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 5 (91.15 g, crude) was obtained as a brown oil. TLC (Ethyl acetate: Methanol = 9:1), R_f = 0.80.

[001350] Preparation of compound 6. A mixture of compound 5 (91 g, 164.75 mmol), Pd/C (28 g, 10% purity) and NaOAc (122.85 g, 1.50 mol) in EtOH (700 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 15 °C for 24 hr under H_2 atmosphere (15 psi). TLC showed compound 5 was consumed and one main spot was found. The Pd/C was filtered off and the filtrate evaporated. The residue was added with water (500 mL), extracted with EtOAc (500 mL*6). And then the organic layer was washed with brine (500 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 6 (76 g, crude) was obtained as a brown oil. TLC (Petroleum ether: Ethyl acetate = 1:3), R_f = 0.12.

[001351] Preparation of compound 7. To a solution of compound 6 (70 g, 164.15 mmol) in MeOH (1000 mL) was added $NH_3.H_2O$ (1.15 kg, 8.21 mol, 1.26 L, 25% purity). The mixture was stirred at 15 °C for 16 hr. TLC indicated compound 6 was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove MeOH and the water phase was extracted with EtOAc (300 mL*8). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 0:1). Compound 7 (33 g, 62.37% yield) was obtained as a white solid. TLC (Ethyl acetate: Methanol = 9:1), R_f = 0.39.

[001352] Preparation of compound 8. To a solution of compound 7 (33 g, 102.38 mmol) in pyridine (120 mL) was added DMTCl (41.63 g, 122.85 mmol). The mixture was stirred at 15 °C for 4 hr. TLC indicated compound 7 was consumed and one new spot formed. The reaction mixture was diluted with sat. $NaHCO_3$ (aq., 100 mL) and extracted with EtOAc (200 mL * 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 1/5, 5% TEA). Compound 8 (55 g, 86.00% yield) was obtained as a yellow solid. TLC (Petroleum ether: Ethyl acetate = 0:1), R_f = 0.65.

[001353] Preparation of WV-SM-47a. A mixture of compound 8 (55 g, 88.04 mmol) , NaOH (42.26 g, 1.06 mol) in DMSO (300 mL) and Water (300 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. LCMS and TLC showed the compound 8 was completed, and one main peak with desired MS 545 (NEG, $M\text{-}H^+$) was found. The reaction mixture was quenched by addition EtOAc (1000 mL), and then diluted with H_2O (1000 mL) and extracted with EtOAc (1000 mL * 4). The combined organic layers were washed with brine (1000 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/ Ethyl acetate = 20/1 to 1/3, 5% TEA). WV-SM-47a (37.5 g, 77.92%

yield) was obtained as a white solid. LCMS (M-H^+) 545.3. TLC (Petroleum ether: Ethyl acetate = 0:1, 5% TEA), R_f = 0.29.

[001354] Preparation of compound 9. To a solution of WV-SM-47a (37.5 g, 68.60 mmol) in DCM (400 mL) was added pyridine (81.40 g, 1.03 mol, 83.06 mL) and Dess-Martin periodinane (34.92 g, 82.33 mmol). The mixture was stirred at 20 °C for 4 hr. LC-MS showed WV-SM-47a was consumed completely and new peak with desired MS was detected. The reaction mixture was quenched by addition sat. $NaHCO_3$ (aq., 1000 mL) and sat. Na_2SO_3 (aq.) 1000 mL, and then extracted with EtOAc (100 mL * 5). The combined organic layers were washed with brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 9 (43 g, crude) was obtained as a yellow solid. LCMS (M-H^+) 543.3.

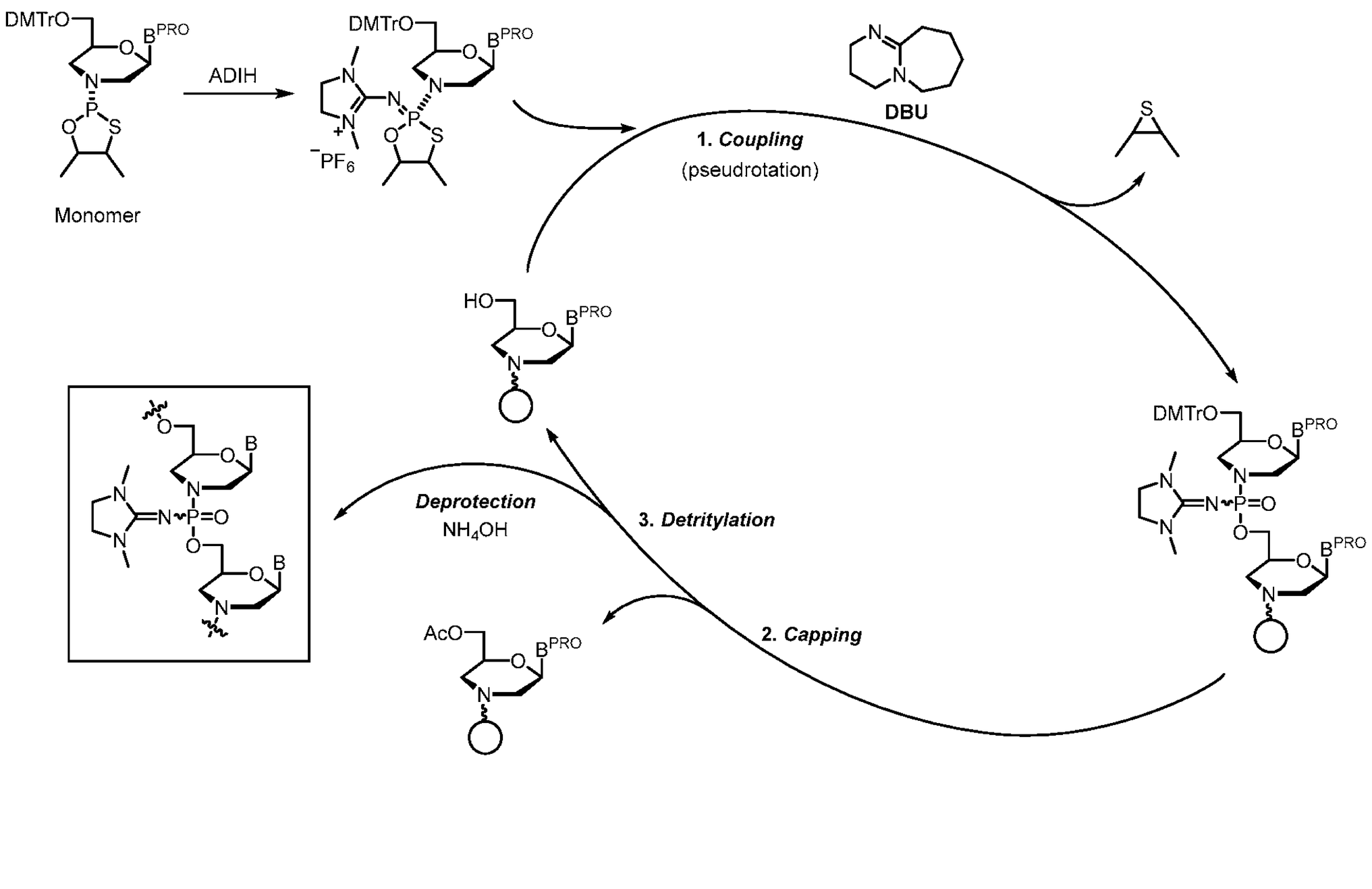
[001355] Preparation of WV-NU-53a and WV-NU-50a. To a solution of compound 9 (37.36 g, 68.60 mmol) in THF (300 mL) was added MeMgBr (3 M, 68.60 mL) at -40 °C. The mixture was stirred at -40-15°C for 6 hr. LC-MS showed compound 9 was consumed completely and new peaks with mass was detected. The reaction mixture was quenched by addition water (20 mL) at 0°C, and then extracted with EtOAc (300 mL * 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. TLC showed one main spot. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate = 20/1 to 0/1, 5% TEA). 6 g of the residue was purified by SFC (column: DAICEL CHIRALPAK AD-H(250mm*30mm,5um);mobile phase: [0.1%NH_3H_2O IPA];B%: 39%-39%,9.33min). And crude WV-SM-50a was purified by prep-HPLC (column: Agela Durashell 10u 250*50mm;mobile phase: [water(0.04%NH_3H_2O)-ACN];B%: 37%-56%,20min). WV-SM-53a (1.4 g, 23.33% yield) was obtained as a white solid. WV-SM-50a (1.8 g, 30.00% yield) was obtained as a white solid. 0.5 g of WV-SM-53a: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.37 - 7.30 (m, 2H), 7.28 - 7.18 (m, 8H), 7.12 (d, J=1.1 Hz, 1H), 6.80 (d, J=8.6 Hz, 4H), 6.08 (q, J=5.8 Hz, 1H), 4.09 - 3.99 (m, 1H), 3.79 (d, J=0.9 Hz, 6H), 3.51 (q, J=5.0 Hz, 1H), 3.20 - 3.05 (m, 2H), 2.70 (q, J=7.1 Hz, 2H), 1.71 (d, J=1.1 Hz, 3H), 1.46 (d, J=6.0 Hz, 3H), 1.14 - 1.10 (m, 3H). ^{13}C NMR (101MHz, CHLOROFORM-d) δ = 163.19, 158.54, 150.48, 144.39, 135.53, 134.91, 129.86, 129.81, 127.90, 127.86, 126.93, 113.15, 111.48, 86.73, 81.44, 81.24, 68.14, 63.45, 55.22, 45.74, 21.45, 18.01, 12.43. HPLC purity: 99.04%. LCMS (M-H^+): 559.0. SFC dr = 99.83: 0.17. TLC (Petroleum ether: Ethyl acetate = 1:3), R_f = 0.28. 0.9 g of WV-SM-53a: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.36 - 7.30 (m, 2H), 7.29 - 7.15 (m, 9H), 7.13 (s, 1H), 6.80 (d, J=8.8 Hz, 4H), 6.08 (q, J=6.0 Hz, 1H), 4.11 - 3.97 (m, 1H), 3.79 (s, 6H), 3.51 (q, J=4.9 Hz, 1H), 3.13 (dq, J=5.3, 10.1 Hz, 2H), 1.72 (s, 3H), 1.47 (d, J=6.2 Hz, 3H), 1.10 (d, J=6.4 Hz, 3H). ^{13}C NMR (101MHz, CHLOROFORM-d) δ = 163.19, 158.54, 150.47, 144.39, 135.50, 134.92, 129.86, 129.81, 127.89, 127.87, 126.94, 113.15, 111.48, 86.73, 81.44, 81.25, 68.14, 63.45, 55.22, 45.19, 21.46, 18.02, 12.44. HPLC purity: 97.56%. LCMS (M-H^+): 559.1, purity 92.9%. SFC dr = 98.49: 1.51. 1.75 g of WV-SM-50a: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.41 (s, 1H), 7.35 - 7.31 (m, 2H), 7.26 - 7.19 (m, 7H), 7.11 (d, J=1.3 Hz, 1H), 6.82 - 6.77 (m, 4H), 6.00 (q, J=5.7 Hz, 1H), 4.09 - 4.00 (m, 1H), 3.79 (d, J=0.9 Hz, 6H), 3.51 - 3.44 (m, 1H), 3.22 (dd, J=5.3, 10.1 Hz, 1H), 3.02 (dd, J=5.3, 10.1 Hz, 1H), 2.20 (br s, 1H), 1.72 (d, J=0.9 Hz, 3H), 1.47 (d, J=6.1 Hz, 3H), 1.17 (d, J=6.6 Hz, 3H).

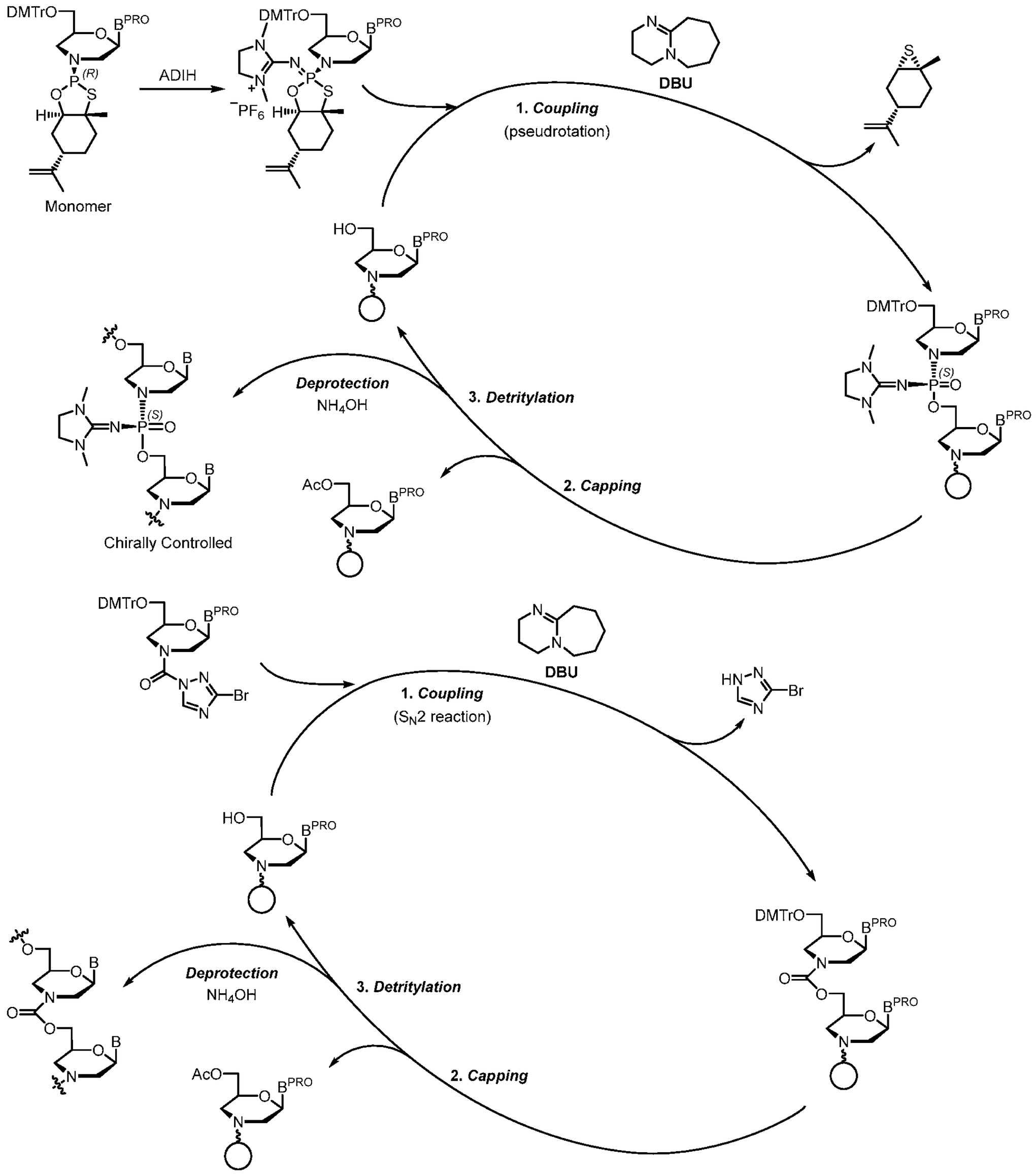
^{13}C NMR (101MHz, CHLOROFORM-d) δ = 163.29, 158.50, 150.43, 144.40, 135.55, 135.45, 134.86, 129.88, 129.84, 127.93, 127.84, 126.94, 113.12, 111.46, 86.55, 82.48, 82.43, 67.59, 63.24, 55.22, 21.40, 19.17, 12.43. HPLC purity: 96.51%. LCMS (M-H$^+$): 559.2, purity 93.04%. SFC dr = 0.88: 99.12.

[001356] Example 3. Preparation of oligonucleotide and compositions.

[001357] Various technologies for preparing oligonucleotides and oligonucleotide compositions (both stereorandom and chirally controlled) can be utilized in accordance with the present disclosure, including, for example, methods and reagents described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the methods and reagents of each of which are incorporated herein by reference. Many oligonucleotides and compositions thereof, e.g., various oligonucleotides and compositions thereof in Table 1, were prepared and assessed and were confirmed to provide various activities, e.g., adenosine editing.

[001358] Certain useful cycles are described below as examples for preparing oligonucleotides.





Each B is independently a nucleobase such as BA described herein (e.g., A, C, G, T, U, etc.). Each B^{PRO} is independently an optionally protected nucleobase such as BA described herein (e.g., A^{bz}, C^{ac}, G^{ibu}, T, U, etc. suitable for oligonucleotide synthesis). As shown, various linkages can be constructed to connect monomers to nucleosides or oligonucleotides including those on solid support. As appreciate by those skilled in the art these cycles can be utilized to couple monomers to −OH of various other types of sugars.

[001359] In some embodiments, preparations include one or more DPSE and/or PSM cycles.

[001360] A number of oligonucleotide compositions were synthesized and assessed. Observed MS data of

oligonucleotides in some prepared oligonucleotide compositions are as follows (when multiple numbers are presented for the same oligonucleotide, the numbers can be MS data observed in different batches/experiments): WV-20666: 10167.1; WV-20689: 10183; WV-20690: 10198.4; WV-20691: 10215.3; WV-20692: 10230.3; WV-20693: 10246.5; WV-20694: 10262.7; WV-20695: 10278.9; WV-20696: 10294.3; WV-20697: 10311.3; WV-20698: 10327; WV-20699: 10342.9; WV-20700: 10358.5; WV-20701: 10376; WV-20702: 10391.1; WV-20703: 10407.5; WV-20704: 10423.6; WV-20706: 10199; WV-20707: 10215.3; WV-20708: 10230.6; WV-20709: 10246.5; WV-20710: 10262.6; WV-20711: 10279.3; WV-20712: 10294.2; WV-20713: 10310.8; WV-20714: 10327; WV-20715: 10342.9; WV-20716: 10358.7; WV-20717: 10246.3; WV-20718: 10262.7; WV-20719: 10278.3; WV-20720: 10294.2; WV-20721: 10311.4; WV-20722: 10327.1; WV-20723: 10342.8; WV-20724: 10358.7; WV-20725: 10374.8; WV-20726: 10391; WV-20727: 10182.9; WV-20728: 10182.7; WV-20729: 10182.7; WV-20730: 10182.9; WV-20731: 10230.8; WV-20732: 10199.1; WV-20733: 10663.7; WV-20734: 10194.7; WV-20735: 10222.7; WV-20736: 10250.5; WV-20737: 10278.3; WV-20738: 10306.7; WV-20739: 10334.8; WV-20740: 10362.9; WV-20741: 10194.8; WV-20742: 10208.5; WV-20743: 10236.8; WV-20744: 10263.9; WV-20745: 10293.1; WV-20746: 10320.4; WV-20747: 10093.9; WV-20748: 10098.1; WV-20749: 10101.9; WV-20750: 10106.4; WV-20751: 10110.5; WV-20752: 10113.5; WV-20753: 10118.3; WV-20754: 10122.6; WV-20755: 10098; WV-20756: 10100; WV-20757: 10104.3; WV-20758: 10107.7; WV-20759: 10111.8; WV-20760: 10116.7; WV-23388: 10098; WV-23395: 10612.3; WV-24111: 10046.8; WV-24112: 10047; WV-24113: 10047; WV-24114: 10046.8; WV-24115: 10047; WV-24116: 10046.8; WV-24117: 10046.9; WV-24118: 10046.8; WV-24119: 10046.9; WV-24120: 10047.1; WV-24121: 10047; WV-24122: 10047.1; WV-24123: 10047; WV-24124: 10047; WV-24125: 10046.9; WV-24126: 10046.9; WV-24127: 10047; WV-24128: 10046.5; WV-24129: 10047; WV-24130: 10046.8; WV-24131: 10046.8; WV-24132: 10047; WV-24133: 10047.1; WV-24134: 10047; WV-24135: 10047; WV-24136: 10046.9; WV-24137: 10047.1; WV-24138: 10047; WV-24139: 10046.8; WV-24140: 10046.4; WV-24141: 10046.9; WV-24142: 10047; WV-24143: 10047.1; WV-24144: 10047; WV-24145: 10047.1; WV-24146: 10046.9; WV-24147: 10046.7; WV-24148: 10047; WV-24149: 10047; WV-24150: 10047.1; WV-24151: 10047.1; WV-24152: 10047.1; WV-24153: 10047.1; WV-24154: 10047.1; WV-24155: 10047.1; WV-24156: 10046.7; WV-24157: 10047; WV-24158: 10047.1; WV-27457: 12613.1; WV-27458: 11954.6; WV-27459: 12631; WV-27460: 11972.7; WV-27521: 10064.1; WV-31133: 10737.8; WV-31134: 10869.1; WV-31135: 10790.3; WV-31137: 10779.4; WV-31138: 10788.2; WV-31139: 10039.1; WV-31140: 10168.8; WV-31141: 10091.0; WV-31143: 10079.0; WV-31144: 10089.6; WV-31632: 10772.7; WV-31633: 10786.6; WV-31634: 10072.7; WV-31635: 10087.2; WV-31748: 10762.5; WV-31749: 10064.4; WV-28788: 10169.1; WV-27458: 11954.6; WV-31940: 10285.5; WV-35741: 12352.0; WV-42028: 10252.9 (calcd. 10254.9); WV-42680: 10293.4 (calcd. 10294.9); WV-44278: 10326.5 (calcd. 10329); WV-44279: 10331.2 (calcd. 10333); WV-44280: 10346.3 (calcd. 10348); WV-44281: 10266.5 (calcd. 10268.9); WV-44282: 10195.8 (calcd. 10197.9); WV-44283: 10200.1 (calcd. 10201.8); WV-44284: 10135.4 (calcd. 10137.8); WV-44285: 10368.2 (calcd. 10369); WV-44286: 10307.1 (calcd. 10308.9); WV-44287: 10235 (calcd. 10237.9); WV-44288:

10175.9 (calcd. 10177.8); WV-44327: 10398.4 (calcd. 10399.1); WV-44328: 10357.7 (calcd. 10359.1). Many others were also prepared, characterized and assessed, e.g., see those in the Figures.

[001361] As described and confirmed herein, technologies of the present disclosure are useful for preparing various compositions of oligonucleotides comprising various structural features. In some embodiments, as confirmed herein, provided technologies, e.g., those utilizing chiral auxiliaries comprising electron-withdrawing groups (e.g., R^{C11} comprising electron-withdrawing groups (e.g., $-SO_2R^{C1}$, $-C(O)R^{C1}$, etc.)) are particularly useful for preparing chirally controlled compositions of oligonucleotides comprising 2'-OH sugars (e.g., sugars with R^{2s} = OH, such as sugars typically found in natural RNA), particularly when such sugars are bonded to chirally controlled internucleotidic linkages. A preparation of WV-29874 is described below as an example.

[001362] An automated solid-phase synthesis of a chirally controlled oligonucleotide composition (WV-29874) at 25 umol scale was performed according to the cycles below:

step	operation	reagents and solvent		volume	waiting time
1	detritylation	3% TCA / DCM		10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN PhIMT / MeCN	0.5M	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN		2.0 mL	2 min
4	sulfurization	0.2M XH / pyridine		2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN MeIm / MeCN	20%	1.0 mL 1.0 mL	45 s

IBN: isobutyronitrile; MeIm: *N*-methylimidazole; PhIMT: *N*-phenylimidazolium triflate; XH: xanthane hydride. The cycles were performed multiple times until the desired length was achieved. PSM phosphoramidites were utilized for formation of chirally controlled internucleotidic linkages (for 2'-OH, protected with TBS (t-butyldimethylsilyl)).

[001363] After completion of the synthesis cycles, PSM chiral auxiliary groups were removed by an anhydrous base treatment (DEA treatment). The CPG was treated with 40% $MeNH_2$ (5.0 mL) for 30 min at 35 °C, then cooled to room temperature and the CPG was separated by membrane filtration, washed with 8.0 mL of DMSO. To the filtrate, TEA (triethylamine)-3HF (5.0 mL) was added and stirred for 1 h at 45 °C which can remove TBS protection groups from 2'-OH. The reaction mixture was cooled to room temperature and diluted with 10 mL of 50 mM NaOAc (pH 5.2). The crude material was analyzed by LTQ and RP-UPLC. The crude materials were purified by RP-HPLC with a linear gradient of MeCN in 50mM TEAA (triethylammonium acetate), desalting by tC18 SepPak cartridge to obtain the target oligonucleotide.

[001364] Desalting was performed using the following procedure:

Evaporate MeCN from samples if present.

Condition column with 4 CV of 100% acetonitrile (HPLC grade).
Rinse column with 2 CV of 40% MeCN in Millipore Bio-Pak water, Endotoxin-Free.
Rinse column with 4 CV of water (Millipore Bio-Pak, Endotoxin-Free).
Equilibrate column with 2 CV of 50 mM TEAA in Millipore Bio-Pak water, Endotoxin-Free.
Load pure fractions onto equilibrated column. In some embodiments, loading by gravity provide the greatest amount of binding, loading slowly with vacuum provide decent binding, and loading quickly with vacuum result in poor binding.
Wash column with 2 CV of BioPak water to wash away TEAA.
Wash column with 2 CV of 100 mM NaOAc to exchange the ammonium on the backbone of oligonucleotides with Sodium instead.
Wash column with BioPak water until conductivity of eluent is <20 uS/cm.
Elute product with 2 column volumes of 40% MeCN in Millipore Bio-Pak water, Endotoxin-Free.
Place on Speed-vac overnight at 30 °C to remove acetonitrile and to concentrated.

[001365] Results from one preparation: Synthesis scale: 25 umol; Crude ODs: 874 ODs; Crude UPLC purity: 32.17%; Crude LTQ purity: 62.45%; Final ODs: 59.8 OD; Final UPLC purity:59.85%; Final MS purity: 74.51%; and Final Observed MS: 10064.4 (Calculated 10,063.68).

[001366] In accordance with the present disclosure, many technologies can be utilized by those skilled in the art to prepare oligonucleotides and compositions of the present disclosure.

[001367] For example, various chirally controlled oligonucleotide compositions were prepared. Certain useful procedures were described below as examples. In some embodiments, oligonucleotides comprises mixed PS (phosphorothioate)/PO(natural phosphate linkage)/PN (e.g., phosphoryl guanidine internucleotidic linkages such as n001) backbone. Oligonucleotides with various numbers of PS/PO/PN linkages (e.g., see Table 1) were prepared using technologies in accordance with the present disclosure. For example, in some embodiments, phosphodiester (PO) linkage were formed using cyanoethyl amidites, phosphorothioate (PS) linkages (*S*p and *R*p; in some embodiments, all *S*p) were formed using DPSE chiral amidites, phosphoroamidate linkages (PN; e.g., n001) (*S*p and *R*p) linkages were formed using PSM amidites. Oligonucleotides typically comprise various sugar modifications, such as 2′-modifications like 2′-OMe, 2’-F and 2′-MOE, etc. (e.g., see Table 1). In some embodiments, oligonucleotides comprise additional moieties such as triantennary GalNAc moiety at, e.g., 5’-end. For introduction of GalNAc moiety at 5’-end, in some embodiments oligonucleotides were synthesized by coupling with C-6 amino modifier as the last coupling cycle and after purification and desalting were conjugated with tri-antennary GalNAc to make conjugates.

[001368] *Example procedure for preparation of oligonucleotide compositions (25 μmol scale)*

[001369] For chirally controlled PS linkages, DPSE amidites were used and for chirally controlled PN linkages such as n001, PSM amidites were used. Automated solid-phase synthesis of oligonucleotides was performed according to cycles shown below: Regular amidite cycle for PO linkages, DPSE amidite cycle for

chirally controlled PS linkages, and PSM amidite cycles for chirally controlled PN linkages such as n001.

Regular Amidite Synthetic Cycle

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN	0.5 mL	8 min
		0.5M CMIMT / MeCN	1.0 mL	
3	oxidation	50mM I_2 / pyridine-H_2O (9:1, v/v)	2.0 mL	1 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN	1.0 mL	45 s
		20% MeIm / MeCN	1.0 mL	

DPSE Amidite Synthetic Cycle

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN	0.5 mL	8 min
		0.5M CMIMT / MeCN	1.0 mL	
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN	1.0 mL	45 s
		20% MeIm / MeCN	1.0 mL	

PSM Amidite Synthetic Cycle

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN	0.5 mL	8 min
		0.5M CMIMT / MeCN	1.0 mL	
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	imidation	0.5M ADIH reagent / MeCN	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN	1.0 mL	45 s
		20% MeIm / MeCN	1.0 mL	

[001370] In some embodiments, for introduction of GalNAc moiety at 5'-end, oligonucleotides were synthesized by coupling with C-6 amino linker as the last coupling cycle.

[001371] *Example procedure for cleavage & de-protection (25 μmol scale)*

[001372] After completion of cycles, the CPG support was treated with 20% diethylamine/acetonitrile wash step for 5 column volume/15 mins followed by ACN wash cycle. The CPG solid support was dried and

transferred into 50 mL plastic tube, and was treated with 1X desilylation reagent (2.5 mL; 100 μL/umol) for 3 h at 28 °C, then added conc. NH_3 (5.0 mL; 200 μL/umol) for 24 h at 37 °C. The reaction mixture was cooled to room temperature and the CPG was separated by membrane filtration and washed with 15 mL of H_2O. The crude material (filtrate) was analyzed by LTQ and RP-UPLC. For certain oligonucleotides to be conjugated with other additional chemical moieties such as GalNac, oligonucleotides comprising suitable reactive groups such as amino groups were purified by ion exchange chromatography on AKTA pure system using a sodium chloride gradient. Desired product was desalted and further conjugated with GalNAc-containing acid. After conjugation reaction was found to be completed, the material was further purified by ion exchange chromatography and desalted using tangential flow filtration (TFF) to obtain desired products (e.g., various oligonucleotide compositions in Table 1 including WV-46312, WV-47606, WV-47608, WV-49085, WV-49086, WV-49087, WV-49088, WV-49089, WV-49090, WV-49092, WV-47603, WV-47604, WV-47605, WV-47607, WV-47609, WV-49091, WV-49093, WV-48453, WV-48454, etc.).

[001373] For example, WV-47595 was prepared and then conjugated to prepare WV-46312. A useful synthesis process is described below as an example.

[001374] In a preparation, synthesis of WV-47595 was performed on AKTA OP100 synthesizer (GE healthcare) using a 3.5 cm diameter fineline column on a 1200 μmol scale using a CPG support (loading 72 μmol/g). Certain synthetic cycles contained five steps: detritylation, coupling, capping 1 (cap-1), oxidation/sulfurization/imidation and capping 2 (cap-2).

[001375] Detritylation: Detritylation was performed using 3% DCA in toluene with a UV watch command set at 436 nm. Following detritylation, the CPG support was subjected to wash cycle using acetonitrile for 2CV.

[001376] Coupling: DPSE and PSM chiral amidites were prepared at 0.2M conc. (in ACN or 20%IBN in ACN). The amidites were mixed in-line with CMIMT activator (0.5M in acetonitrile) at a ratio of 5.83 prior to addition to the column. The coupling mixture was recycled for 10 minutes to maximize the coupling efficiency followed by column wash with 2CV of ACN. Cyanoethyl amidites were prepared at 0.2M conc. (in ACN or 20%IBN in ACN). The amidites were mixed in-line with ETT activator (0.5M in acetonitrile) at a ratio of 4.07 prior to addition to the column. The coupling mixture was recycled for 10 minutes to maximize the coupling efficiency followed by column wash with 2CV of ACN.

[001377] Capping 1: For stereodefined couplings, the column was then treated with Capping 1 solution (acetic anhydride, lutidine, ACN) for 1 CV in 2 minutes which can acetylate the chiral auxiliary amine. Following this step, the column was washed with 1.5 CV of acetonitrile. For stereorandom coupling Capping 1 was not performed.

[001378] Sulfurization/Imidation/Oxidation step: Sulfurization was performed with 0.1 M xanthane hydride in pyridine/acetonitrile (1.2 equivalent) with a contact time of 6 minute followed by 2CV wash step. Imidation was performed with 0.3 M ADIH reagent in acetonitrile with 18 equivalent and 15 min contact time followed

by 2CV wash step. Oxidation step was performed using oxidation reagent (50mM I_2 / pyridine-H_2O (9:1, v/v)) 3.5 eq. 2.5 minute followed by 2CV acetonitrile wash.

[001379] Capping 2: Capping 2 step was performed using Capping A and Capping B reagents mixed inline (1:1) (e.g., see cap-2) followed by a 2 CV ACN wash.

[001380] After completion of the synthesis, the CPG support was finally treated with 20% diethylamine/acetonitrile wash step for 5 column volume/15 mins followed by ACN wash cycle. The CPG solid support was dried and transferred into pressure vessel. DPSE were removed by treating the support with desilylation reagent at a ratio of per µmole support/100 µL desilylation reagent. The desilylation reagent was made by mixing DMSO : water : TEA : TEA.3HF in ratio of 7.33:1.47:0.7:0.5. The CPG support was incubated in presence with desilylation reagent for 3 hours at 27 °C in an incubator shaker. After that conc. ammonia was added at a ratio of per µmole support/200 µL of conc. ammonia. The mixture was incubated and shaken for 24 hours at 37 °C. The mixture was cooled and filtered using 0.2-0.45 micron filter and the CPG support was rinsed three times to collect all the desired material as filtrate. The filtrate containing crude oligonucleotides was analyzed by RP-UPLC and quantitation was done using a Nanodrop One Spectrophotometer (Thermo Scientific) and a yield of 110,000 OD/µmole was obtained.

[001381] Purification and desalting: Crude oligonucleotides were loaded on to Waters AP-2 glass column (2.0 cm x 20 cm) packed with Source 15Q (Cytiva). Purification was performed on an AKTA150 Pure (GE healthcare) using the following buffers: (Buffer A: 20 mM NaOH, 20% Acetonitrile v/v) (Buffer B: 20 mM NaOH, 2.5M NaCl, 20% Acetonitrile v/v). Desired fractions with full length products in the range of 70-80% were pooled together. The pooled material was then desalted on a 2KD re-generated cellulose membrane followed by lyophilization to obtain oligonucleotides as a fluffy white cake ready for conjugation.

[001382] Preparation of WV-46312: Various technologies can be utilized to conjugate oligonucleotides with other moieties in accordance with the present disclosure. A useful protocol for GalNAc conjugation is described below as an example. Pre-conjugation material: WV-47595.01 (.01 denoting the batch number). Product material: WV-46312.01.

Reagent	Mol. Wt. for present protocol	Equivalent	Volume (mL)
WV-47595	10050.80	1	-
Tri-antennary GalNAc acid	2006	1.8	-
HATU	382	1.4	-
DIEA	129	10	-
Acetonitrile		-	4

Aqueous oligonucleotide solution			
Oligonucleotide solution	Conc. (mg/mL)	Total volume (mL)	Total (mg)
WV-47595 in WFI water	50	8	400

[001383] The tri-antennary GalNAc acid (hydroxyl groups protected as −OAc) and HATU are weighed out in a 50 mL plastic tube and dissolved in anhydrous acetonitrile then DIEA was added into the tube. The

resulting mixture was stirred for 10 min at 37 °C. Lyophilized WV-47595 was reconstituted in water in a separate tube and the GalNAc mixture was added to the oligonucleotide solution and stirred for 60 min at 37 °C. The reaction was monitored by RP-UPLC. Reaction was found to be complete in 1 h. The reaction mixture was concentrated under vacuum to remove the acetonitrile and the resultant GalNAc-conjugated oligonucleotides was treated with conc. ammonia for 2 h at 37°C. The formation of final product was confirmed by mass spectrometry and RP-UPLC. The conjugated material was purified by anion exchange chromatography and desalted using tangential flow filtration (TFF) to obtain the final product (Target mass: 12110.65; Observed mass: 12112.3). Using similar procedures various oligonucleotides and compositions were manufactured.

[001384] Example 4. Provided technologies can provide products with improved properties and/or activities.

[001385] As described herein, in some embodiments, provided technologies can correct mutations and provide improved or restored levels, properties and/or activities of various products such as proteins. For example, in some embodiments, provided technologies correct mutations and provide proteins, e.g., wild-type proteins with improved or restored levels, properties and/or activities. In some embodiments, provided technology provided increased levels of desired proteins, e.g., proteins of improved properties and/or activities compared to corresponding proteins prior to administration of provided technologies (e.g., oligonucleotides, compositions, etc.). In some embodiments, provided technologies provide increased levels of wild-type proteins. In some embodiments, provided technologies provide increased levels of properly folded proteins. Among other things, the present disclosure provides data confirming various such benefits, using editing of 1024 G>A in SERPINA1 as an example.

[001386] In some embodiments, cells, tissues or animals comprising 1024 G>A mutation in human SERPINA1 was utilized to assess provided technologies. In some embodiments, an animal is NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(SERPINA1*E342K)#Slcw/SzJ mouse (e.g., see The Jackson Laboratory Stock No: 028842; NSG-PiZ, and also Borel F; Tang Q; Gernoux G; Greer C; Wang Z; Barzel A; Kay MA; Shultz LD; Greiner DL; Flotte TR; Brehm MA; Mueller C. 2017. Survival Advantage of Both Human Hepatocyte Xenografts and Genome-Edited Hepatocytes for Treatment of alpha-1 Antitrypsin Deficiency. Mol Ther 25(11):2477-2489PubMed: 29032169MGI: J:243726, and Li S; Ling C; Zhong L; Li M; Su Q; He R; Tang Q; Greiner DL; Shultz LD; Brehm MA; Flotte TR; Mueller C; Srivastava A; Gao G. 2015. Efficient and Targeted Transduction of Nonhuman Primate Liver With Systemically Delivered Optimized AAV3B Vectors. Mol Ther 23(12):1867-76PubMed: 26403887MGI: J:230567). In some embodiments, cells, tissues or organs from such an animal were utilized to assess provided technologies.

[001387] In some embodiments, primary murine hepatocytes were plated into wells of 96 well plates, one plate for each time point being interrogated. After a suitable time period, e.g., 24 hours, oligonucleotide compositions were administered, e.g., in some embodiments, cells were transfected with an oligonucleotide composition at 25nM final oligonucleotide concentration using a suitable technology, e.g., RNAiMAX as

manufacturer's instruction. Media was collected for protein analysis (e.g., using ELISA), and cells were collected for RNA editing analysis (e.g., in RNA Lysis buffer (Promega) for later sequencing), at suitable time points, e.g., 120 hours.

[001388] ELISA. In some embodiments, A1AT protein concentration was assessed using a A1AT ELISA assay, e.g., Abcam - ab108799 assay in accordance with manufacturer's instructions. In some embodiments, standards were generated using recombinant A1AT protein diluted to 25 ng/ml in a diluent and serially diluted 2-fold for 7 points. Cell culture media was cleared by centrifugation at 3000g for 10 minutes before being diluted 1 to 400 in a diluent. Prepared standards and diluted culture media were added to the wells of a SERPINA1 antibody coated and blocked 96 well plate and incubated for 2 hours at room temperature. Plates were washed with provided ELISA wash buffer 6 times (300 uL/well) before a biotinylated SERPINA1 antibody was diluted to 1X in a diluent and added to each well for 1 hour at room temperature. Wells were washed as previously described, and a streptavidin-peroxidase complex, diluted to 1X in a diluent, was added to each well for 30 minutes at room temperature. Wells were washed a final time before 3,3',5,5'-Tetramethylbenzidine (TMB) is added to each well and the plate was developed for 20 minutes before stop solution was added. The plate was then read at 450 nm and 570 nm. The reading at 570 nm was subtracted from the 450 nm reading to account for optical imperfections and the plate was quantified. Certain data were presented in Figure 1.

[001389] As confirmed in Figure 1, provided technologies can provide editing of mutations associated with conditions, disorders or diseases, e.g., a PiZ mutation of SERPINA1 (SA1). Among other things, provided technologies not only provide editing on RNA levels, they can also provide improved levels, properties and/or activities of proteins. For example, as shown in Figure 1, in addition to RNA editing, provided technologies can provide increased levels of secreted proteins (e.g., WV-38621, WV-38622 and WV-38630 compared to non-targeting (NT) control WV-37317) which can include proteins of improved folding and/or higher activities compared to proteins encoded by unedited RNA (e.g., proteins comprising E342K mutation)from 1024G>A mutation)). As appreciated by those skilled in the art, levels, properties and/or activities, including sequences, may also be assessed using other technologies such as mass spectrometry. In some embodiments, LC-MS based proteomics technologies are utilized to quantitate A1AT proteins (e.g., wild-type and/or mutant proteins (e.g., encoded by RNA with or without editing)).

[001390] Example 5. Various oligonucleotide compositions can provide editing.

[001391] Various oligonucleotides were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were designed to either have a majority of 2'-F modified sugars in a domain (5') and a majority of 2'-OMe modified sugars in another domain (3'), or a majority of 2'-OMe modified sugars in a domain (5') and a majority of 2'-F in another domain (5'). Oligonucleotide compositions were then screened in either 293T or ARPE19 cells that stably expressed the SERPINA1-PIZ allele. As shown in Figure 2 (a) and (b), certain oligonucleotide compositions comprising certain sequences, and/or lengths of 5'- and/or 3'-sides of nucleosides opposite to target adenosines (e.g., C), provide higher levels of editing. In some embodiments

WV-42028 and WV-42029 gave higher editing levels than WV-42027 in all three cell lines, 293T-SERPINA1-ADAR1-p110p110, 293T-SERPINA1-p150, and ARPE19-SERPINA1. In some embodiments, as shown in Figure 2 (a) and (b), when an edit site is moving from one domain to another domain, moving surrounding 2' chemistry (e.g., 2'-OMe modified sugars) may improve editing efficiency. In some embodiments, it was observed that when an editing site is in a domain (5'), it may be helpful to have the domain comprising multiple 2'-OMe modified sugars (and optionally another domain comprising multiple 2'-F modified sugars).

[001392] Example 6. Various oligonucleotide compositions can provide editing.

[001393] Various oligonucleotides were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were designed to contain a 8-oxo-dA base modification in a domain (3'). Oligonucleotides were then screened in either 293T or SF8628 cells that stably expressed SERPINA1-PIZ allele. In some embodiments, WV-42680 and WV-42681 gave higher editing levels than WV-42679 in all three cell lines, 293T-SERPINA1-ADAR1-p110, 293T-SERPINA1-p150, and SF8628-SERPINA1 (Figure 3).

[001394] Example 7. Various oligonucleotide compositions can provide editing.

[001395] Oligonucleotides comprising various modified nucleobases (e.g., b008U) and/or various types of sugars (e.g., DNA sugars, RNA sugars, etc.) at or around editing sites were designed around a PIZ target site and assessed. Oligonucleotide compositions were screened in either 293T or SF8628 cells that stably expressed SERPINA1-PIZ allele. In some embodiments, WV-38621, WV-38622, WV-28923, WV-42328, WV-38629, WV-38630, and WV-42327 gave higher editing levels than WV-38620 in 293T-SERPINA1-ADAR1-p110, 293T-SERPINA1-p150, and SF8628-SERPINA1 (Figure 4).

[001396] Example 8. Various oligonucleotide compositions can provide editing.

[001397] Oligonucleotides comprising various base sequences, modified sugars (*e.g.*, 2'-F, 2'-OMe, etc), and/or modified internucleotide linkages (*e.g.*, neutral internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages, etc.) were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were administered via GalNAc mediated uptake at multiple dose concentrations in primary mouse hepatocytes expressing human SERPINA1-PIZ. As shown in Figure 5, various oligonucleotides can provide editing activities. In some embodiments, as shown in Figure 5, addition of one or more 2'F modified sugars, e.g., in domain-2 (3'), may increase editing efficiency.

[001398] Example 9. Various oligonucleotide compositions can provide editing.

[001399] Oligonucleotides comprising various types of sugars including modified sugars (*e.g.*, 2'-F, 2'-OMe, etc.), and modified internucleotide linkages (*e.g.*, non-negatively charged internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages) were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were administered via gymnotic uptake at multiple dose concentrations in primary mouse hepatocytes expressing human SERPINA1-PIZ. In some embodiments, as shown in Figure 6, various oligonucleotides can provide editing activities.

[001400] Example 10. Various oligonucleotide compositions can provide editing.

[001401] Oligonucleotides comprising modified bases (*e.g.*, 8-oxo-dA), various types of sugars including

modified sugars (*e.g.*, 2'-F, 2'-OMe, etc.), and/or modified internucleotide linkages (*e.g.*, non-negatively charged internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages, etc.) were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were administered via gymnotic uptake in primary mouse hepatocytes expressing human SERPINA1-PIZ. In some embodiments, WV-42680, WV-42935, and WV-42938 displayed greater editing efficiency compared to WV-42028. In some embodiments, as shown in Figure 7, modified bases (*e.g.*, 8-oxo-dA), certain sugars (*e.g.*, arabino-cytidine), or combinations thereof may demonstrate increased editing efficiency.

[001402] Example 11. Various oligonucleotide compositions can provide editing.

[001403] Oligonucleotides comprising modified bases (*e.g.*, 8-oxo-dA), various types of sugars including modified sugars (*e.g.*, 2'-F, 2'-OMe, etc.), and/or modified internucleotide linkages (*e.g.*, non-negatively charged internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages, etc.) were designed and assessed. Certain oligonucleotides can target a PIZ target site. Oligonucleotides were administered in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. In some embodiments, WV-42680 and WV-42028 displayed higher editing levels as compared to WV-42679 and WV-42027. In some embodiments, as shown in Figure 8, shifting a target sequence by 1nt may increase editing efficiency. In some embodiments, inclusion of a modified base (*e.g.*, 8-oxo-dA) may increase editing efficiency.

[001404] Example 12. Various oligonucleotide compositions can provide editing.

[001405] Oligonucleotides comprising modified bases (*e.g.*, 8-oxo-dA), various types of sugars including modified sugars (*e.g.*, 2'-F, 2'-OMe, etc.), and/or modified internucleotide linkages (*e.g.*, non-negatively charged internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages, etc.) were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. In some embodiments, WV-43112, WV-431113, and WV-43114 displayed higher editing levels as compared to WV-42680. See Figure 9. In some embodiments, addition of 2'-F modified sugars to an oligonucleotide, e.g., in domain-2 (3'), may increase editing activity. In some embodiments, addition of 2'-OMe modified sugars at a 5' end of may improve editing efficiency.

[001406] Example 13. Various oligonucleotide compositions can provide editing.

[001407] Oligonucleotides comprising modified bases, various types of sugars including modified sugars (*e.g.*, 2'-F, 2'-OMe, etc.), and/or modified internucleotide linkages (*e.g.*, non-negatively charged internucleotidic linkages such as n001, phosphorothioate internucleotidic linkages, etc.) were designed and assessed. Certain oligonucleotides can target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 10, in some embodiments, various oligonucleotides comprising modified internucleotide linkages at various positions can provide editing activities. In some embodiments, oligonucleotides with non-negatively charged internucleotidic linkages such as n001 at certain positions provide higher activities compared to others.

[001408] Example 14. Various oligonucleotide compositions can provide editing.

[001409] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 11, in some embodiments, Rp phosphorothioate internucleotide linkages can be incorporated at various locations to provide oligonucleotides with editing activities, and at certain sites may increase editing levels.

[001410] Example 15. Various oligonucleotide compositions can provide editing.

[001411] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 12, in some embodiments, addition of 2'-F modified sugars to certain sites, e.g., in a domain comprising multiple 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe modified sugars) such as domain-2 (3') in certain oligonucleotides, may increase or maintain editing levels.

[001412] Example 16. Various oligonucleotide compositions can provide editing.

[001413] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 13, in some embodiments, addition of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe modified sugars) to certain sites in, e.g., a domain comprising multiple 2'-F modified sugars such as domain-1 (5') in certain oligonucleotides, may increase or maintain editing levels. In some embodiments, 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe modified sugars) are utilized at 5'- and/or 3'-ends of oligonucleotides.

[001414] Example 17. Compositions of oligonucleotides of various lengths can provide editing.

[001415] Oligonucleotides comprising various modifications and base sequences and of different lengths (*e.g.*, 28 nt, 29 nt, 30 nt, 31 nt, 32 nt) were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 14, oligonucleotides of various lengths including those significantly shorter than reported by others can provide editing activities. In some embodiments, 31 nt and 32 nt oligonucleotides can provide improved editing levels.

[001416] Example 18. Compositions of oligonucleotides comprising various types of internucleotidic linkages can provide editing.

[001417] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 15, in some embodiments, natural phosphate linkages, non-negatively

charged internucleotidic linkages such as n001 and phosphorothioate internucleotidic linkages can be utilized various positions to provide editing. In some embodiments, natural phosphate linkages at certain sites, e.g., certain positions of domain-2 (3'), may increase editing levels. In some embodiments, certain combinations of various internucleotidic linkages and/or stereochemistry at certain sites can increase editing levels.

[001418] Example 19. Various oligonucleotide compositions can provide editing.

[001419] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by GalNAc mediated uptake. As shown in Figure 16, various oligonucleotides can provide editing activities. In some embodiments, addition of addition of 2'-OR modified sugars wherein R is optionally substituted C_{1-6} aliphatic (e.g., 2'-OMe modified sugars) at 5'- and/or 3'-ends of oligonucleotides may increase editing levels.

[001420] Example 20. Various oligonucleotide compositions can provide editing.

[001421] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. GalNAc-conjugated oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ. As shown in Figure 17, various oligonucleotides can provide editing activities. In some embodiments, oligonucleotides comprising increased levels of 2-'F modified sugars and/or certain bases/nucleobases (*e.g.*, 8-oxo-dA, b001A, b008U, I, etc.) at certain positions may provide increased editing levels.

[001422] Example 21. Provided editing regions can improve editing.

[001423] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof, and various editing regions including various sequences around a nucleoside opposite to a target adenosine, were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic mediated uptake. As shown in Figure 18 (a)-(c), various oligonucleotides can provide editing activities. In some embodiments, certain mismatches or wobble base pairs at 5' and/or 3' nearest positions to an edit site may reduce editing levels compared to fully complementary editing regions. In some embodiments, certain mismatches or wobble base pairs at 5' and/or 3' nearest positions to an edit site in some embodiments maintain or increase editing levels.

[001424] Example 22. Various oligonucleotide compositions can provide editing.

[001425] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic mediated uptake. As shown in Figure 19, various oligonucleotides can provide editing activities. In some embodiments, introduction of a 2'-DNA nucleoside (e.g., T instead of 2'-F U) adjacent to an edit site (e.g., as N_1) may increase editing levels.

[001426] Example 23. Various oligonucleotide compositions can provide editing.

[001427] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic mediated uptake. Various such oligonucleotide can provide editing activities. As shown in Figure 20, in some embodiments, increasing levels of 2'-F modified sugars may increase editing levels.

[001428] Example 24. Oligonucleotides of various provided designs can provide editing.

[001429] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. As shown in Figure 21, oligonucleotides comprising various types of sugars (e.g., DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (e.g., natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof) and stereochemistry (e.g., *R*p, *S*p, and patterns thereof) and patterns thereof can provide editing activities. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. In some embodiments, certain oligonucleotides provide higher editing levels compared to others.

[001430] Example 25. Various oligonucleotide compositions can provide editing.

[001431] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. As shown in Figure 22, oligonucleotides comprising various types of sugars (e.g., DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (e.g., natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof) and stereochemistry (e.g., *R*p, *S*p, and patterns thereof) and patterns thereof can provide editing activities. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. In some embodiments, certain oligonucleotides provide higher editing levels compared to others.

[001432] Example 26. Various oligonucleotide compositions can provide editing.

[001433] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. As shown in Figure 23, oligonucleotides comprising various types of sugars (e.g., DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (e.g., natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof) and stereochemistry (e.g., *R*p, *S*p, and patterns thereof) and patterns thereof can provide editing activities. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-

PIZ by gymnotic uptake. In some embodiments, certain oligonucleotides provide higher editing levels compared to others. In some embodiments, 2'-OR modified sugar wherein R is not hydrogen (e.g., when R is optionally substituted C_{1-6} aliphatic) such as 2'-OMe modified sugars at 5' and/or 3' terminus. In some embodiments, oligonucleotides comprise non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) at both 5'- and 3'-end. In some embodiments, oligonucleotides comprise non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) at 5'-end. In some embodiments, oligonucleotides comprise non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) at 3'-end.

[001434] Example 27. Various oligonucleotide compositions can provide editing.

[001435] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. As shown in Figure 24, oligonucleotides comprising various types of sugars (e.g., DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (e.g., natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof) and stereochemistry (e.g., *R*p, *S*p, and patterns thereof) and patterns thereof can provide editing activities. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. In some embodiments, certain oligonucleotides provide higher editing levels compared to others. In some embodiments, 2'-OR modified sugar wherein R is not hydrogen (e.g., when R is optionally substituted C_{1-6} aliphatic) such as 2'-OMe or 2'-MOE modified sugars at 5' and/or 3' terminus. In some embodiments, oligonucleotides comprise non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001) at 5'- and/or 3'-end. In some embodiments, natural DNA sugars may be utilized at an end region (e.g., 5'-end region as shown in Figure 24) with modified internucleotidic linkages, such as non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001), phosphorothioate internucleotidic linkages, etc.

[001436] Example 28. Various oligonucleotide compositions can provide editing.

[001437] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotides target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 25, various oligonucleotides comprising various types of sugars, nucleobases and internucleotidic linkages, including various nucleobases, sugars, nucleosides at and/or around a nucleoside opposite to a target adenosine (e.g., b001A, b001rA, Csm15, I, etc.) can provide editing activities. In some embodiments, certain oligonucleotides provide higher editing levels.

[001438] Example 29. Various oligonucleotide compositions can provide editing.

[001439] In some embodiments, oligonucleotides comprise mismatches and/or wobble base pairs when

aligned with target nucleic acids. As demonstrated herein, various such oligonucleotides can provide editing activities. In some embodiments, oligonucleotides comprising G-U wobble base pairs at certain positions were designed to target a PIZ target site. Oligonucleotides were tested in primary mouse hepatocytes expressing human SERPINA1-PIZ by gymnotic uptake. As shown in Figure 26, in various embodiments, oligonucleotides comprising G-U wobble base pairs provide editing activities.

[001440] Example 30. Various oligonucleotide compositions can provide editing.

[001441] Oligonucleotides comprising various types of sugars (e.g., DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (e.g., natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof) and stereochemistry (e.g., *R*p, *S*p, and patterns thereof) and patterns thereof, including various structural features at editing regions (e.g., various types of sugars, nucleobases, nucleosides, linkages, etc., such as 5MRm5dC, 5MSm5dC, 5MSm5fC, fC, dC, m5dC, dA, 5MSdT, 5MRdT, etc., for N_1, N_0, N_{-1}, N_{-2}, etc.) can provide editing activities. In some embodiments, oligonucleotides comprising 5'-(R)-Me or 5'-(S)-Me modified sugars provide editing activities. Certain data were presented in Figure 27. Oligonucleotides were tested in primary human hepatocytes by GalNAc mediated uptake at various concentrations

[001442] Example 31. Various oligonucleotide compositions can provide editing.

[001443] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages and stereochemistry and patterns thereof were designed and assessed. Certain oligonucleotide target an ACTB target site. Oligonucleotides were tested in primary human hepatocytes by GalNAc mediated uptake at various concentrations. As shown in Figure 28, various oligonucleotides including those comprising non-negatively charged internucleotidic linkages such as *n001 and/or UNA (Unlocked Nucleic Acids) sugars can provide editing activities.

[001444] Example 32. Various oligonucleotide compositions can provide editing.

[001445] In some embodiments, oligonucleotides comprise 5'-caps. In some embodiments, oligonucleotides comprise abasic 5'-caps. In some embodiments, oligonucleotides comprise additional chemical moieties, e.g., connected to 5'-ends of oligonucleotides. Various such oligonucleotides were prepared and accessed. In some embodiments, oligonucleotides were tested in primary human hepatocytes by GalNAc mediated uptake. As shown in Figure 29, such oligonucleotides can provide editing activities.

[001446] Example 33. Certain editing regions provide high editing levels.

[001447] Among other things, the present disclosure provides editing regions that are particularly useful for editing. In some embodiments, the present disclosure provides 5'-$N_1N_0N_{-1}$–3' elements that are particularly useful for editing. In some embodiments, they are fully complementary to target adenosines and nucleosides directly 5' and 3' thereto. In some embodiments, they comprise one or more mismatches and/or wobble base pairs. In some embodiments, those comprising mismatches and/or wobble base pairs, including at N_{-1} and/or N_1, provide comparable or higher levels of editing compared absence of such mismatches and/or wobble base

pairs. In some embodiments, oligonucleotides comprising various nucleosides directly 5' and 3' to and at an edit sites were designed and assessed, targeting an ACTB target as an example. In some embodiments, plasmid reporters expressing full-length ACTB cDNA with various combinations of nucleosides directly 5' and 3' to target adenosine were designed and tested with corresponding oligonucleotides, each featuring unique combinations of bases and/or sugars directly 5' and 3' to edit site. Plasmids and oligonucleotides were tested in 293T cells by transfection. As shown below, in some embodiments, oligonucleotides comprising certain mismatches and/or wobble base pairs directly 5' and/or 3' to an edit site may maintain or increase editing levels. Combinations of nearest neighbors for each target are denoted horizontally on top of the chart (5' to 3' orientation) and combinations of nearest neighbors for edit site in oligonucleotides are denoted vertically on left of chart (3' to 5'). Endogenous ACTB transcript is denoted with *. Opposite to target adenosine in oligonucleotides are dC. Mean editing values for each reporter-oligonucleotide combination are plotted. For top to bottom oligonucleotides are WV-42331 to WV-42335, WV-37317, WV-42337 to WV-42349.

	A_A	A_U	A_G	A_C	U_A	U_U	U_G	U_C	G_A	G_U	G_G	G_C	C_A	C_U	C_G	C_C	U_G*
T_U	51.8	22.3	58.9	17.1	29.0	0.9	28.2	2.7	29.5	2.1	22.6	0.9	5.9	2.1	4.4	1.6	8.0
T_A	20.2	51.3	28.4	35.9	3.0	27.0	3.5	2.9	4.7	23.4	4.1	1.8	1.8	8.8	3.1	2.5	1.4
T_C	50.5	25.5	58.4	12.3	11.9	2.5	60.2	1.0	30.5	3.0	40.7	2.4	1.6	1.7	22.3	1.2	37.0
T_G	32.6	46.1	36.7	51.2	3.4	11.4	5.4	45.2	20.6	7.8	14.5	27.3	4.2	4.3	4.6	12.5	1.9
A_U	36.4	4.7	42.1	4.8	65.4	51.6	70.3	55.6	37.4	3.8	28.0	2.6	12.6	1.7	12.9	1.8	75.1
A_A	4.4	43.7	6.3	8.7	52.4	63.5	54.0	61.0	6.7	29.3	5.4	3.3	7.4	12.8	2.3	4.3	42.3
A_C	23.0	3.3	52.7	2.2	69.0	57.7	75.2	57.1	38.7	5.2	48.3	4.0	6.5	0.4	36.2	3.8	78.7
A_G	5.4	16.6	17.4	43.2	56.9	60.9	67.2	71.3	21.1	13.5	16.7	40.5	2.2	4.9	4.0	20.0	61.5
C_U	38.2	10.8	41.6	13.6	30.6	20.6	37.6	29.2	36.0	6.8	37.1	9.6	13.9	10.2	25.3	12.3	17.6
C_A	4.4	44.9	7.3	9.8	3.4	31.6	3.2	5.3	15.3	19.1	19.9	9.7	1.2	7.5	1.7	0.0	2.8
C_C	24.9	3.3	52.7	3.2	9.9	1.5	54.3	1.3	50.8	9.9	41.2	3.8	3.4	1.3	21.7	2.4	27.0
C_G	4.8	17.0	15.5	48.3	3.7	6.2	9.2	43.7	16.5	16.1	20.2	24.6	0.7	0.6	2.2	7.9	3.5
I_U	56.2	16.7	60.2	9.5	57.9	15.0	66.3	12.0	46.7	6.0	38.3	2.4	52.2	45.0	56.6	36.4	47.0
I_A	6.6	55.9	13.1	19.0	8.2	56.0	17.2	19.0	8.3	38.6	8.4	4.1	35.3	54.8	45.0	44.5	4.3
I_C	45.7	12.6	60.7	5.2	49.5	14.5	64.6	11.2	46.3	6.2	48.8	4.7	48.8	42.9	58.3	32.3	69.2
I_G	18.9	42.9	39.4	53.0	16.2	43.7	39.5	70.0	33.3	22.5	27.6	49.3	39.0	54.0	54.3	52.3	18.0
G_U	48.6	8.5	47.7	4.6	34.2	7.3	37.9	3.9	53.4	7.3	45.8	3.1	42.9	25.9	58.5	21.0	12.4
G_A	5.1	47.8	8.1	9.9	3.7	32.2	5.8	7.9	11.1	42.4	12.0	7.2	24.7	48.1	38.6	30.1	1.4
G_C	36.9	7.5	62.7	4.3	37.3	5.3	57.2	2.6	52.1	10.7	49.9	4.1	49.8	29.8	57.6	20.3	35.0
G_G	10.2	29.3	24.8	53.5	7.0	18.6	16.9	49.6	32.2	31.3	29.9	49.7	33.6	37.3	49.8	46.6	7.5

[001448] Example 34. Various oligonucleotide compositions can provide editing.

[001449] In some embodiments, oligonucleotides comprise 5'-caps. In some embodiments, oligonucleotides comprise abasic 5'-caps. In some embodiments, oligonucleotides comprise additional chemical moieties, e.g., connected to 5'-ends of oligonucleotides. Various such oligonucleotides were prepared and accessed. In some embodiments, oligonucleotides then tested in primary mouse hepatocytes expressing human ADAR-p110. As shown in Figure 30, such oligonucleotides can provide editing activities.

[001450] Example 35. Provided technologies can provide editing in vivo.

[001451] Among other things, the present disclosure demonstrate that provided oligonucleotides can provide editing in vivo. In an example, non-Human-Primates (NHP) were dosed with a single subcutaneous (SC) dose of WV-37317 at 50mg/kg (3X Macaca fascicularis) or with PBS as a control (1X Macaca fascicularis). Dosing details are shown below. Animals where sacrificed day 8 (dose on day 1, collection on day 8), and all tissues where collected for PK/PD analysis. As shown in Figure 31, (a), multiple tissues (kidney, liver, lung, heart, pancreases, pulmonary vein and artery, duodenum, ileum, jejunum, PBMCs) displayed ACTB editing and WV-37317 was detected at high levels in all tissues (see Figure 31, (b)). Among other things, oligonucleotides of the present disclosure can be delivered, e.g., by SC administration, in NHPs, allowing for broad tissue distribution and efficient endogenous ADAR mediated editing in multiple tissue types.

Group	TA	Description	Strain	Gender	Dose	Dosing Regimen	Dose Volume	NHP #	Necropsy
1	PBS	NA	Cynomolgus monkey, naïve Asian original	1M	n/a	s.c. (Day 1)	1 ml/kg	1	Day 8
2	WV-37317	ACTB		2M, 1F	50 mpk	s.c. (Day 1)	1 ml/kg	3	Day 8

[001452] Example 36. Provided technologies can provide editing in vivo.

[001453] Among other things, the present disclosure demonstrate that provided oligonucleotides can provide editing in vivo. In an example, non-Human-Primates (NHP) were dosed with a single intrathecal (IT) dose of WV-37317 at either 10mg or 5mg (6X Macaca fascicularis) or with PBS as a control (1X Macaca fascicularis). Dosing details are shown below. The animals where sacrificed at either day 8 or 29 (dose on day 1, collections at days 8 and 29), and tissues where collected for PK/PD analysis. As shown in Figure 32, (a), multiple tissues (e.g., spinal cord, cortex, hippocampus, midbrain, cerebellum, corpus callosum, and optic nerve, etc.) displayed ACTB editing. As shown in Figure 32, (b), WV-37317 was detected in various CNS tissues. Among other things, oligonucleotides of the present disclosure can be delivered, e.g., by IT administration in NHPs, and provide broad distribution and efficient endogenous ADAR mediated editing in various tissues including CNS tissues.

Group	Test Article	Description	Dose (mg)	Dose Regimen	Total # per group	Gender	Necropsy time point

1	PBS	control	NA	IT x 1	1	M	Day 8
2	WV-37317	SP-PN	5		2	M/F	Day 8
3	WV-37317	SP-PN	10		2	M/F	Day 8
4	WV-37317	SP-PN	10		2	M/F	Day 29

[001454] Example 37. Various oligonucleotide compositions can provide editing.

[001455] In some embodiments, oligonucleotides comprise duplexing and targeting oligonucleotides. In some embodiments, such oligonucleotides can form duplexes with, e.g., duplexing nucleic acids and oligonucleotides. In some embodiments, oligonucleotides and corresponding duplexing oligonucleotides. In some embodiments, oligonucleotides were designed to target a luciferase reporter target and assessed. In some embodiments, designs combined two oligonucleotide pieces sharing a 16 bp or 18 bp complementary sequence, allowing association of both pieces within cells. Certain oligonucleotides were tested in combination by transfection in 293T cells. Editing efficiency was calculated by determining cLUC/gLUC ratios. As shown in Figure 33, in some embodiments certain combinations of oligonucleotide pieces can provide editing. Certain duplex designs were provided in Figure 35 as examples. As those skilled in the art appreciates, various suitable lengths may be utilized for portions, regions, oligonucleotides, etc. in accordance with the present disclosure.

[001456] Example 38. Various oligonucleotide compositions can provide editing.

[001457] In some embodiments, an oligonucleotide comprises a stem loop as well as double and single-stranded regions. In some embodiments, such an oligonucleotide can be utilized as a duplexing oligonucleotide to form complexes with an oligonucleotide comprising a duplexing and a targeting region. An example design were shown in Figure 35. As those skilled in the art appreciates, various suitable lengths may be utilized for portions, regions, oligonucleotides, etc. in accordance with the present disclosure. As an example, certain oligonucleotides were designed to target a site in a luciferase reporter construct. Designs combined two oligonucleotides sharing a complementary sequence (e.g., 15 bp), allowing association of both pieces and formation of a stem loop complex within cells. Oligonucleotides were tested in combination by transfection in 293T cells. Editing efficiency was calculated by determining cLUC/gLUC ratios. As shown in Figure 34, various combinations provide editing activities.

[001458] Example 39. Various oligonucleotide compositions can provide *in vivo* editing.

[001459] Among other things, provided technologies can provide *in vivo* edition. In some embodiments, oligonucleotides (e.g., WV-43120, WV-44464, WV-44465) were shown to confirm *in vivo* editing of the SERPINA1-Z allele in human ADAR (huADAR) transgenic mice described herein. Thirty-two male mice of the JAX huADAR x SA1 mouse line were used, all heterozygous for SA1-PiZ. Of those, twenty mice were also heterozygous for huADAR-p110, and twelve mice were wild-type for mouse ADAR (no expression of huADAR-p110). UGP2 was used as a control for huADAR activity. Mice were dosed subcutaneously (s.c.) with 10 mg/kg of selected oligonucleotide or PBS control every other day for three days (Days 0, 2, 4). Serum

was collected from the mice prior to dosing and on Day 7 following treatment, and liver biopsies were collected on Day 7. Samples were subjected to PK and PD analyses and hybrid ELISA. Certain information was provided below:

TA	Description	Strain	Gender	Dose	Dosing Regimen	Mice #
PBS	NA	- Het for SA1-PiZ - Het for huADAR-p110	M	n/a	s.c. (Day 0,2,4)	4
WV-43120	SA1-PiZ		M	10 mpk	s.c. (Day 0,2,4)	4
WV-44464	SA1-PiZ		M	10 mpk	s.c. (Day 0,2,4)	4
WV-44465	SA1-PiZ		M	10 mpk	s.c. (Day 0,2,4)	4
WV-38702	UGP2		M	10 mpk	s.c. (Day 0,2,4)	4
PBS	NA	- Het for SA1-PiZ - WT for mouse ADAR (no expression of huADAR-p110)	M	10 mpk	s.c. (Day 0,2,4)	4
WV-44464	SA1-PiZ		M	10 mpk	s.c. (Day 0,2,4)	4
WV-44465	SA1-PiZ		M	10 mpk	s.c. (Day 0,2,4)	4

[001460] In some embodiments, primary mouse hepatocytes from the transgenic model (expressing human ADARp110 and human SERPINA1-Z allele) were treated with various GalNAc-conjugated oligonucleotides for 48 hrs. RNA editing was measured by Sanger sequencing. In some embodiments, as shown in Figure 36, various oligonucleotides provided *in vitro* editing of the SERPINA1-Z allele.

[001461] Liver biopsy samples collected on Day 7 from the huADAR/SA1 transgenic mice underwent Sanger sequencing to measure percent editing. In some embodiments, as confirmed in Figure 37, various oligonucleotide compositions provided *in vivo* editing activity up to about 20%, up to about 30%, or up to about 40% for the SERPINA1-Z allele.

[001462] From serum samples collected from mice prior to dosing and on Day 7 following treatment, concentration of total human AAT in serum was determined by a commercially available ELISA kit (AbCam). In some embodiments, as shown in Figure 38, *in vivo* editing from dosing various oligonucleotides increased total human AAT concentration in serum.

[001463] From serum samples collected from mice prior to dosing and on Day 7 following treatment, the relative abundance of Z (mutant) vs. M (wild-type) AAT isoforms was determined by mass spectrometry. Absolute amounts of each isoform were then calculated by applying relative abundances to absolute concentrations obtained from ELISA (see Figure 38). In some embodiments, as confirmed in Figure 39, editing from treatment with WV-44464 resulted in secretion of wild-type AAT protein and a substantial decrease of mutant Z-AAT protein in serum. As confirmed herein, in some embodiments, provided technologies can increase wild-type SERPINA1 protein levels in blood. In some embodiments, provided technologies can decrease mutant SERPINA1 protein levels in blood. In some embodiments, as shown in Figure 38, about 75% of total AAT in blood is wild-type.

[001464] Certain data were present below as examples.

In vivo SERPINA1-Z allele editing in huADAR mice (e.g., Figure 37):

ID	PBS	WV-43120	WV-44464

Editing	1.4	0	1.38	0	15	16	18.7	17.6	39.8	38.8	36.4	37.2
ID	WV-44465				WV-38702 (UGP2 control)							
Editing	29.8	33.2	26	28.4	0	0.12	0	0				

Human AAT concentration in serum (ELISA) (e.g., Figure 38):

ID	Pre Dose				Day 7			
PBS	256.527	266.166	239.436	235.305	127.656	177.39	182.655	193.914
WV-38702	280.017	252.153	298.485	217.242	194.643	247.293	217.242	177.633
WV-43120	208.656	239.274	269.73	189.783	241.38	365.472	387.666	255.636
WV-44464	296.703	303.507	325.296	247.941	527.229	493.695	572.508	463.077
WV-44465	280.26	193.104	195.615	187.353	417.96	410.67	372.762	356.643

AAI isoforms in serum (Mass spectrometry; PBS and WV-44464) (e.g., Figure 39):

	PiM (WT)				PiZ (E342K mutant)			
Pre-dose	0.21	0.24	0.24	0.21	256.32	265.93	239.2	235.09
Day 7	0.13	0.16	0.14	0.16	127.53	177.23	182.52	193.75
Pre-dose	0.31	0.13	0.28	0.17	296.39	303.37	325.02	247.77
Day 7	385.89	346.79	392.73	316.84	141.34	146.91	179.77	146.24

Elastase inhibition activity in serum (e.g., Figure 40)

ID	Pre Dose				Day 7			
PBS	19.52	23.94	34.47	23.75	18.28	30.92	46.04	30.03
WV-43120	17.89	15.23	21.31	15.16	35.29	36.63	36.9	21.82
WV-44464	33.11	27.94	26.44	23.85	64.01	73.62	79.2	67.21
WV-44465	36.58	29.43	23.4	25.86	58.68	57.7	43.65	50.53
WV-38702	33.78	25.74	35.88	35.71	23.57	28.97	32.29	26.03

[001465] It was confirmed that provided technologies can provide editing and functional proteins. From serum samples collected from mice prior to dosing and on Day 7 following treatment, relative elastase inhibition activity was determined using a commercially available kit (EnzChek® Elastase Assay Kit (E-12056)). Diluted serum was incubated with recombinant elastase enzyme and fluorescently tagged elastin substrate. Activity of elastase enzyme can be detected by fluorescence signal detected upon elastin cleavage. Relative inhibition was calculated about a control reaction with no serum present (100% elastase activity). Each sample was run in technical replicate. Among other things, data shown in Figure 40 confirmed that wild-type AAT protein produced and secreted as a result of editing by provided technologies was functional, e.g., for elastase inhibition.

[001466] Among other things, data presented herein confirm that transgenic mouse models expressing human ADAR are useful for assessing ADAR editing agents, e.g., oligonucleotides. In some embodiments, as confirmed herein, up to 40% or more editing of SERPINA1 Z allele mRNA were provided (e.g., in liver at

certain time points). In some embodiments, provided editing levels are nearing correction to heterozygotes (MZ). In some embodiments, as confirmed herein, provided technologies provide significant increase in circulating functional wild-type M-AAT protein *in vivo*. In some embodiments, provided technologies reduce levels of mutant Z-AAT protein in, e.g., liver, serum, etc.

[001467] Example 40. Provided technologies can modulate protein-protein interactions.

[001468] As confirmed herein, provided technologies among other things can modulate protein-protein interactions, e.g., through adenosine editing in mRNA and changing identities of amino acid residues in polypeptides encoded thereby. In some embodiments, provided technologies modulate protein-protein interactions, activities, and/or functions by, e.g., editing one or more amino acid residues of one or more proteins. As demonstrated herein, editing of various residues of Keap1 or Nrf2 can modulate their interactions, activities and/or functions. For example, in some embodiments, editing of residues of Keap1 or Nrf2 increase levels of Nrf2, transcription of nucleic acids that can be activated by Nrf2 and/or expression of Nrf2-regulated genes. Keap1 has been reported to NRF2 and mediate NRF2 proteasomal degradation. In some embodiments, disrupting interactions between Keap1 and NRF2 allows post-transcriptional upregulation of NRF2 and translocation of NRF2 to the nucleus, where it may activate transcription of NRF2-regulated genes. As demonstrated herein, various oligonucleotides were designed to target specific editing sites in either Keap1 or Nrf2 transcripts. As shown in Figure 41, (a), various oligonucleotides can provide editing at multiple sites in Keap1 or NRF2 transcripts. In some embodiments, editing of Keap1 and/or Nrf2 transcripts may alter expression levels of downstream genes regulated by NRF2 (*e.g.*, SRGN, HMOX1,SLC7a11, NQO1, etc., as shown in Figure 41, (b)). In some embodiments, oligonucleotides provide editing of Keap1 or NRF2 transcripts that change amino acid residues, which can disrupt of Keap1 / NRF2 complex formation and stability, and modulate NRF2 levels, translocation and/or expression of nucleic acids regulated by NRF2. In some embodiments, certain oligonucleotides provide higher editing levels compared to others. In some embodiments, oligonucleotides comprise non-negatively charged internucleotidic linkages (*e.g.*, phosphoryl guanidine internucleotidic linkages such as n001) at a 5'- and/or 3'-end. In some embodiments, oligonucleotides comprise 2'-OR modified sugars wherein R is not hydrogen (*e.g.*, wherein R is optionally substituted C_{1-6} aliphatic) such as 2'-OMe modified sugars at 5'- and/or 3'-end. In some embodiments, oligonucleotides comprise 2'-F modified sugars at 5'- and/or 3'-end. Those skilled in the art appreciate that various oligonucleotide designs described herein may be applied for modulating interactions between polypeptides.

[001469] Example 41. Provided technologies can provide robust durable editing *in vivo*.

[001470] In some embodiments, the present disclosure provides oligonucleotide compositions that can, among other things, provide editing activities in various systems, *e.g.*, in various cells, tissues, and/or organs *in vivo*. Certain data are presented in Figure 42, confirming that provided technologies can provide durable editing in various tissues *in vivo*, including in CNS. Human ADAR (hADAR) transgenic mice described herein were treated with a single 100 ug dose of WV-40590 oligonucleotide composition through

intracerebroventricular (ICV) injection. Mice were sacrificed at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 16 weeks post-dose and multiple CNS tissues were collected and analyzed. As shown in Figure 42, UGP2 mRNA editing was achieved in all tissues analyzed. In some embodiments, UGP2 editing levels were comparable across various time points analyzed. Among other things, these data demonstrate that provided technologies can provide effective editing of various tissues *in vivo* for at least 16 weeks.

[001471] Example 42. Provided technologies can provide editing.

[001472] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages, and stereochemistry and patterns therefor were designed and assessed. Certain oligonucleotides target specific editing sites in UGP2 transcripts. As shown in Figure 43 and Figure 44, oligonucleotides comprising various types of sugars (*e.g.*, DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (*e.g.*, natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof), and stereochemistry (*e.g.*, Rp, Sp, and patterns thereof) and patterns thereof can provide editing activities. In some embodiments, 2'-F in second domains (e.g., in regions to the 3'-side of N_0; in some embodiments, from N_{-2} to 3'-end of an oligonucleotide) and/or natural phosphate linkages and/or 2'-OR wherein R is C_{1-6} optionally substituted aliphatic (e.g., 2'-OMe, 2'-MOE, etc.) in first domains (e.g., in regions to the 5'-side of N_0; in some embodiments, from 5'-end of an oligonucleotide to N_2) and/or in second domains provide improved editing efficiency. Oligonucleotides were tested in human hepatocytes by gymnotic uptake (Figure 43) and IPSC derived neurons (Figure 44). In some embodiments, certain oligonucleotides provide higher editing compared to others at specific concentrations.

[001473] Example 43. Provided technologies can provide editing in vivo.

[001474] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages, stereochemistry, additional chemical moieties, etc. and patterns therefor were designed and assessed. Certain oligonucleotides target specific editing sites in UGP2 transcripts. As shown in Figure 45, provided oligonucleotide compositions can provide editing activities in various tissues *in vivo*, including in liver. Oligonucleotides were tested in wild-type (Wt) and transgenic hADAR mice through subcutaneous administration of 3 doses of 10 mg/kg (0, 2, and 4 days, respectively). In some embodiments, certain oligonucleotide compositions provide higher editing compared to others. In some embodiments, certain oligonucleotide compositions provide much higher editing in hADAR mice compared to wt mice. In some embodiments, certain oligonucleotide compositions provide high editing levels in both wt and hADAR mice.

[001475] Example 44. Provided technologies can provide editing in various cell populations.

[001476] In some embodiments, the present disclosure provides oligonucleotide compositions that can, among other things, provide editing activities in various systems, *e.g.*, in various cells, tissues, and/or organs. Certain data are presented in Figure 46, confirming that provided technologies can provide editing in various immune cell populations including PBMCs. Among other things, provided technology can provide editing in cell populations such as CD4+, CD8+, CD14+, CD19+, NK, Treg cells, etc. Cells were treated with 10 uM

WV-37317 under activating (addition of PHA) or non-activating conditions. RNA was isolated 4 days post-treatment through benchtop antibody/bead protocols. As shown in Figure 46, ACTB mRNA editing was achieved in multiple immune cell populations. In some embodiments, ACTB editing levels were comparable for activated and non-activated cell populations. In some embodiments, ACTB editing levels were increased for activated cell populations.

[001477] Example 45. Provided technologies can provide editing in vivo.

[001478] In some embodiments, the present disclosure provides oligonucleotide compositions that can, among other things, provide editing activities in various systems, *e.g.*, in various cells, tissues, and/or organs *in vivo*. Certain data are presented in Figure 47, confirming that provided technologies can provide editing *in vivo* including in eyes. A single 10 ug or 50 ug ICV injection of WV-40590 oligonucleotide composition was administered in posterior compartment of eye of transgenic hADAR mice. RNA was isolated 1 week and 4 weeks post-treatment. As shown in Figure 47, robust UGP2 mRNA editing was achieved in eye at both doses.

[001479] Example 46. Provided technologies can provide durable editing in vivo.

[001480] Among other things, provided technologies can provide durable editing *in vivo*. Certain data are presented in Figure 48, confirming that provided technologies can provide durable editing in a mouse model. Wild-type and transgenic hADAR mice were treated with PBS or 10 mg/kg of WV-44464 oligonucleotide composition at days 0, 2, and 4. Serum was collected through weekly blood draws and levels of total human AAT protein (total, wild-type (M-AAT), and mutant (Z-AAT)) were quantified by ELISA and mass spectrometry. As shown in Figure 48, provided technologies can increase total human AAT serum concentration, and can generate or increase wild-type AAT protein (M-AAT). In some embodiments, it was observed AAT serum concentrations were ≥3-fold higher over 30 days post last dose (Figure 48, (a)). In some embodiments, restored wild type M-AAT was detected over 30 days post last dose (Figure 48, (b)).

[001481] Example 47. Provided technologies can provide editing.

[001482] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages, and stereochemistry and patterns therefor were designed and assessed, confirming that oligonucleotides of various designs can provide efficient editing, including those comprising alternating blocks comprising 2'-F and blocks comprising 2'-OR wherein R is C_{1-6} aliphatic (2'-OMe and/or 2'-MOE) blocks, natural phosphate linkages, phosphorothioate internucleotidic linkage internucleotidic linkages, non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001s), controlled stereochemistry, patterns thereof, etc. as described herein. As shown in Figure 49 and Figure 51, oligonucleotides comprising various types of sugars (*e.g.*, DNA sugars, 2'-F modified sugars, 2'-OR modified sugars wherein R is not hydrogen, and patterns thereof), nucleobases (modified and unmodified bases and patterns thereof), internucleotidic linkages (*e.g.*, natural phosphate linkages, non-negatively charged internucleotidic linkages, phosphorothioate internucleotidic linkages, and patterns thereof), and stereochemistry (*e.g.*, Rp, Sp, and patterns thereof) and patterns thereof can provide robust editing activities. Primary mouse hepatocytes transgenic for hADAR p110 and SERPINA1-Z allele were treated with GalNAc-conjugated oligonucleotides

via gymnotic uptake. RNA was harvested 48 hours post-treatment and RNA editing was measured by Sanger sequencing (n=2 biological replicates). Certain EC50 (nM) data were provided below (Figure 49 and Figure 51):

ID	EC50	95% CI (nM)	ID	EC50	95% CI (nM)
WV-44464	13.67	8.574 - 21.50	WV-46323	4.951	2.790 - 8.281
WV-46312	5.139	3.347 - 7.647	WV-46312	3.52	2.98-4.04
WV-46313	4.304	2.59 - 6.778	WV-47606	3.38	2.78-3.96
WV-46314	6.179	2.798 - 12.54	WV-47608	2.44	1.91-2.96
WV-46315	7.121	3.471 - 13.75	WV-49085	2.70	2.13-3.26
WV-46316	6.957	4.929 - 9.661	WV-49086	2.81	2.28-3.34
WV-46317	5.34	3.743 - 7.471	WV-49087	4.53	3.61-5.43
WV-46318	9.433	6.306 - 13.89	WV-49088	4.03	3.23-4.83
WV-46319	6.068	2.971 - 11.57	WV-49089	6.14	5.06-7.21
WV-46320	7.058	3.923 - 12.17	WV-49090	2.46	2.14-2.76
WV-46321	9.851	5.987 - 15.84	WV-49092	3.47	2.97-3.96
WV-46322	6.574	4.944 - 8.657			

[001483] Example 48. Provided technologies can provide editing in vivo.

[001484] Oligonucleotides comprising various types of sugars, nucleobases, internucleotidic linkages, and stereochemistry and patterns therefor were designed and assessed, including those comprising alternating blocks comprising 2'-F and blocks comprising 2'-OR wherein R is C_{1-6} aliphatic (2'-OMe and/or 2'-MOE) blocks, natural phosphate linkages, phosphorothioate internucleotidic linkage internucleotidic linkages, non-negatively charged internucleotidic linkages (e.g., phosphoryl guanidine internucleotidic linkages such as n001s), controlled stereochemistry, patterns thereof, etc. as described herein. Certain data are presented in Figure 50, confirming that provided technologies can provide robust editing in a mouse model. Male and female transgenic hADAR mice were treated with indicated oligonucleotides at 5 mg/kg via subcutaneous administration at days 0, 2, and 4. Liver biopsies were collected at day 7 post-treatment and RNA editing was measured by Sanger sequencing (n=3 animals per gender). As shown in Figure 50, provided oligonucleotide compositions can provide high editing levels. In some embodiments, certain oligonucleotide compositions may provide higher editing levels in male mice as compared to female mice.

[001485] Example 49. Provided technologies can provide edited polypeptides with desired properties and functions in vivo

[001486] In some embodiments, the present disclosure provides oligonucleotide compositions that can, among other things, provide editing activities in various systems, *e.g.*, in various cells, tissues, and/or organs *in vivo* and generate polypeptides with desired properties and activities, e.g., in some embodiments, wild-type proteins. Certain data are presented in Figure 52, confirming that provided technologies in some embodiments can provide editing in a mouse model, and/or can produce increased levels of circulating proteins including wild-type proteins in serum. Wild-type and transgenic hADAR mice were treated with PBS or 10 mg/kg of WV-46312 oligonucleotide composition at days 0, 2, and 4. Serum was collected through weekly blood draws

and levels of total human AAT protein (wild-type (PiM), and mutant (PiZ) were quantified by ELISA and mass spectrometry. As shown in Figure 52, provided technologies can increase AAT serum concentration by about 4-fold or more, and can generate high levels of wild-type AAT in serum, relative to a reference (*e.g.*, pre-dose levels).

[001487] Example 50. Provided technologies can provide editing *in vitro* and *in vivo*.

[001488] Among other things, the present example provides data further confirming that provided technologies can provide editing.

[001489] For example, Figure 53 confirms that oligonucleotides comprising various modifications including various base modifications as described herein (e.g., s b001A, b001rA, CSM15, b008U, etc.) can edit target adenosines. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). RNA editing was quantified by Sanger sequencing.

[001490] Figure 54 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising modified nucleobase such as b008U in the position across the target adenosine edit site, various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing.

[001491] Figure 55 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising modified nucleobase such as b001A in the position across the target adenosine edit site, various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. As confirmed, non-negatively charged internucleotidic linkages such as phosphoryl guanidine internucleotidic linkages like n001 can be utilized in various positions; *R*p phosphorothioate internucleotidic linkages and natural phosphate linkage can also be utilized. In some embodiments, first domains comprise one or more *R*p phosphorothioate internucleotidic linkages, one or more non-negatively charged internucleotidic linkages such as phosphoryl guanidine internucleotidic linkages like n001 (each optionally and independently in *R*p configuration) and one or more natural phosphate linkages. In some embodiments, as shown in various Figures, hypoxanthine is utilized in place of G when close to N_0, e.g., at position N_{-1}.

[001492] Figure 56 confirms that various modifications can be utilized in accordance with the present

disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising modified nucleobase such as b001A, b008U, b010U, b001C, b008C, b011U, b002G, b012U, etc. in the position across the target adenosine edit site, various types of modified linkages (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to be able to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. It was observed that certain base modifications can provide higher editing levels under the conditions tested.

[001493] Figure 57 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising modified nucleobase such as b008U, b010U, b001C, b008C, b011U, and b012U (e.g., at N_1, N_0, etc.), various types of modified linkages (e.g., PS (phosphorothioate), PN (e.g., phosphoryl guanidine linkages such as n001), etc.) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to be able to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. It was observed that certain base modifications can provide higher editing levels under the conditions tested.

[001494] Figure 58 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising modified nucleosides such as Usm04, Csm04, and rCsm13 at N_0 and/or N_1 were assessed and confirmed to provide editing of target adenosines in certain instances. In some embodiments, it was observed that certain modifications (*e.g.*, those comprising UNA sugars such as sm04) at N_0 and/or N_1 provided lower editing levels compared to other modifications under the tested conditions. RNA editing was quantified by Sanger sequencing.

[001495] Figure 59 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various modifications such as Csm11, Csm12, b009Csm11, b009Csm12, Gsm11, Gsm12, Tsm11, Tsm12, L010, etc. (e.g., at one or more of N_1, N_0 and N_{-1} positions) were assessed and confirmed to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. In some embodiments, oligonucleotides comprising natural DNA sugars at N_{-1} and/or N_0 provide higher editing levels compared to those comprising acyclic sugars. In some embodiments, acyclic sugars such as sm11, sm12, etc., can be utilized at N_1.

[001496] Figure 60 confirms that various modifications can be utilized in accordance with the present

disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various modifications and patterns thereof as described herein can provide robust editing. For example, in some embodiments, N_0 sugars whose 2'-groups are independently selected from −H and −OH can provide robust editing (e.g., natural DNA sugar, sm15, etc.). In some embodiments, a N_1 sugar is a natural DNA sugar or a 2'-F modified sugar. In some embodiments, oligonucleotides comprising a 2'-F modified or a natural DNA sugar at N_1 position and natural DNA sugars at N_0 and N_{-1} positions can provide high editing levels. RNA editing was quantified by Sanger sequencing.

[001497] Figure 61 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising increased levels of 2'-OMe modified sugars and PO linkages may provide comparable or increased editing activity relative to a reference at certain concentrations. RNA editing was quantified by Sanger sequencing. As demonstrated, 2'-OR modified sugars wherein R is not −H (e.g., 2'-OMe modified sugars) can be utilized at various positions, including the first and last several nucleosides, first domains, first subdomains, third subdomains, etc. In some embodiments, about 30%-80% (e.g., about 30%-75%, 30%-70%, 30%-65%, 30%-60%, 30%-50%, 40%-70%, 40%-65%, 40%-60%, 40%-50%, or about 30%, 40%, 50%, 60%, 65%, or 70%) of all sugars in an oligonucleotide are each independently a 2'-OR modified sugar wherein R is not −H (e.g., 2'-OMe, 2'-MOE, 2'−O−L^B−4' modified sugars). In some embodiments, about 30%-80% (e.g., about 30%-75%, 30%-70%, 30%-65%, 30%-60%, 30%-50%, 40%-70%, 40%-65%, 40%-60%, 40%-50%, or about 30%, 40%, 50%, 60%, 65%, or 70%) of all sugars in an oligonucleotide are each independently a 2'-OMe or 2'-MOE modified sugar. In some embodiments, about 30%-80% (e.g., about 30%-75%, 30%-70%, 30%-65%, 30%-60%, 30%-50%, 40%-70%, 40%-65%, 40%-60%, 40%-50%, or about 30%, 40%, 50%, 60%, 65%, or 70%) of all sugars in an oligonucleotide are each independently a 2'-OMe modified sugar. In some embodiments, oligonucleotides comprise one or more (e.g., 1-10, 2-10, 3-9, 3-8, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) natural phosphate linkages. In some embodiments, natural phosphate linkages are utilized internally (e.g., not bonded to the first and the last 1, 2 or 3 nucleosides). In some embodiments, at least about 50%, 60%, 70%, 75%, 80%, 85%, or 90% of natural phosphate linkages are each independently bonded to at least one sugar comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2'-MOE, etc.).In some embodiments, natural phosphate linkages are each independently bonded to at least one sugar comprising a 2'-OR modification wherein R is not −H (e.g., 2'-OMe, 2'-MOE, etc.).

[001498] Figure 62 confirms that various modifications can be utilized in accordance with the present

disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of nucleobases, linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to provide editing of target adenosines. As shown herein, 2'-OR modifications wherein R is not −H (e.g., 2'-OMe) can be utilized at various positions in first domains, first subdomains, and/or third subdomains. RNA editing was quantified by Sanger sequencing.

[001499] See, e.g., also Figure 63, Figure 64, Figure 65, Figure 66, Figure 67, Figure 68, Figure 69 and Figure 70 for additional data confirming that sugar modifications, e.g., 2-OR modifications wherein R is not −H (such as 2'-OMe, 2'-MOE, etc.), 2'-F, etc., can be utilized with various other structural elements in accordance with the present disclosure to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-MOE modified sugars, 2'-F modified sugars, natural DNA sugars, etc.) were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising increased levels of 2'-OMe and/or 2'-MOE modified sugars and PO linkages provide comparable or increased editing of target adenosines relative to a reference at certain conditions. RNA editing was quantified by Sanger sequencing.

[001500] Figure 71 further confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, sm15, etc.) were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising sm15 or natural RNA sugar at N_{-2} may provide robust editing under certain conditions. RNA editing was quantified by Sanger sequencing.

[001501] As described herein, various modified charged internucleotidic linkages can be utilized in accordance with the present disclosure. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is n001. In some embodiments, a modified internucleotidic linkage has the structure of −OP(O)(−N(R')SO_2R")O− or a salt thereof wherein each of R' and R" is independently as described herein.

In some embodiments, R' is R as described herein. In some embodiments, R' is −H or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is −H. In some embodiments, a modified internucleotidic linkage has the structure of −OP(O)(−$NHSO_2R$")O− or a salt thereof wherein R" is as described herein. In some embodiments, R" is R as described herein wherein R is not −H. In some embodiments, R" is optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R" is optionally substituted phenyl. For example, in some embodiments, R" is 4-methylphenyl. In some embodiments, R" is 4-($CH_3C(O)NH)C_6H_4$. In some embodiments, R" is optionally substituted C_{1-6} aliphatic. In some embodiments, R" is optionally substituted C_{1-6} alkyl. In some embodiments, R" is methyl. In some embodiments, R" is ethyl. In some embodiments, R" is n-propyl. In some embodiments, R" is isopropyl. In some embodiments, R" is n-butyl. In some embodiments, a linkage is n002. In some embodiments, a linkage is n006. In some embodiments, a linkage is n020. In some embodiments, as confirmed in Figure 72, such internucleotidic linkages may be utilized in place of phosphoryl guanidine internucleotidic linkages such as n001. For example, in some embodiments, such internucleotidic linkages are utilized at 5′-end and/or 3′-end. In some embodiments, such linkages are utilized internally. For example, in some embodiments, such internucleotidic linkages may be utilized between nucleosides N_{-1} and N_{-2}. For Figure 72, primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). RNA editing was quantified by Sanger sequencing.

[001502] In some embodiments, morpholine units may be utilized in place of natural sugars. Figure 73 confirms that such modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, morpholine sugars, etc.) were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising morpholine sugars and various modifications (*e.g.*, Gsm01, Tsm01, Tsm01n013, Gsm01n013, Tsm18) provide comparable or reduced editing of target adenosines relative to a reference at certain concentrations. RNA editing was quantified by Sanger sequencing.

[001503] Figure 74 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various base modifications (*e.g.*, b001A, b008U, etc.), types of linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and various types of sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, morpholine sugars, etc.) were assessed and confirmed to provide editing of target

adenosines. In some embodiments, oligonucleotides comprising morpholine sugars and various modifications (*e.g.*, Gsm01, Tsm01, Csm01, Csm01n013, Tsm01n013, Gsm01n013, Tsm18) provide comparable or reduced editing of target adenosines relative to a reference at certain concentrations. RNA editing was quantified by Sanger sequencing.

[001504] Dose response for various oligonucleotide compositions were assessed. Certain results for certain compositions are presented below as examples. Primary mouse (transgenic for humanADARp110 and SERPINA1-Z allele) hepatocytes were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs. RNA editing was quantified by Sanger sequencing. Oligonucleotides comprising various modifications were assessed and confirmed to provide editing of target adenosines. Serial dilution concentrations from about 1000 nM to about 0.5 nM. About 15%-40% editing observed at the lowest concentration and about 85% editing observed at the highest concentrations.

ID	Absolute EC50 (nM)	95% CI (nM)
WV-46312	7.74	1.09 - 14.39
WV-46313	4.19	1.88 - 6.51
WV-47597	6.74	4.45 - 9.03
WV-47598	7.02	3.53 - 10.52
WV-47599	6.73	4.44 - 9.02
WV-47600	8.24	6.18 - 10.29
WV-47601	5.03	3.61 - 6.45
WV-47602	3.76	1.32 - 6.2
WV-47603	6.93	5.21 - 8.66
WV-47604	8.01	6.17 - 9.85
WV-47605	6.98	4.01 - 9.95
WV-47606	4.32	3.19 - 5.46
WV-47607	4.89	1.3 - 8.48
WV-47608	3.26	0.41 - 6.11
WV-47609	10.71	7.38 - 14.04
WV-44464	10.70	6.11 - 15.29

[001505] Among other things, the present disclosure provides various nearest neighbor pairs that are not perfect matches at both N_1 and N_{-1} positions yet can provide robust, in some embodiments, comparable to or better than perfect matches. Figure 75 shows an example. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). RNA editing was quantified by Sanger sequencing.

[001506] Figure 76 confirms that various modifications can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various modifications (*e.g.*, in b008U, b012U, b013U, b001A, b002A, b003A, b004I, b002G, b009U, etc.) were assessed and confirmed to provide editing of target adenosines. In some

embodiments, oligonucleotides comprising a modified base (*e.g.*, b008U, b012U, b013U, b001A, b002A, b003A, b004I, b002G, b009U, etc.) across from the edit site (position N_0) provided comparable or increased editing activity as compared to a reference. RNA editing was quantified by Sanger sequencing.

[001507] As described herein, various sugars and nucleobases may be utilized at positions including N_1 Figure 77 confirms that various such sugars and/or nucleobases, including modified sugars and/or nucleobases, can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various nucleobases and sugars at N_1, *e.g.*, in dT, b002A, b003A, b008U, b001C, Tsm11, Tsm12, b004C, b007C, etc., were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising such sugars and/or nucleobases at N_1 position provided robust editing activity under certain conditions. RNA editing was quantified by Sanger sequencing. Additional data are presented in Figure 78 confirming that various sugars and nucleobases may be utilized at N_1 in combination with other structural elements (e.g., various sugars, nucleobases, internucleotidic linkages, stereochemistry, etc.) in accordance with the present disclosure to provide editing. For Figure 78, primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various sugars and nucleobases at N_1, *e.g.*, in dT, b003A, b008U, b001C, b008C, Tsm11, Tsm12, b004C, Csm17, etc., were assessed and confirmed to provide editing of target adenosines. In some embodiments, oligonucleotides comprising such sugars and/or nucleobases at N_1 position provided robust editing activity under certain conditions. RNA editing was quantified by Sanger sequencing. As shown in various Figures, in many embodiments, natural and/or modified nucleobases (e.g., C, b008U, etc.) and/or natural DNA sugar are utilized at N_0, and/or natural and/or modified nucleobases (e.g., hypoxanthine) and/or natural DNA sugar are utilized at N_{-1}.

[001508] Similarly, the present disclosure describes various useful sugars and nucleobases for utilization at N_{-1} and useful internucleotidic linkages that can be utilized for connecting N_{-1} to its neighboring nucleosides. For example, Figure 79 confirms that various sugars, nucleosides, internucleotidic linkages, etc. can be utilized to provide editing. Primary hepatocytes were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs. Oligonucleotides comprising various sugars and nucleobases at N_{-1} (*e.g.*, in dI, b001A, b003A, b008U, b001C, b008C, Tsm11, Tsm12, b004C, Csm17, etc.), various linkages (e.g., PS (phosphorothioate) or PN (e.g., phosphoryl guanidine linkages such as n001) linkage between N_{-1} and N_{-2} (e.g., *R*p, *S*p or stereorandom), PS linkage between N_0 and N_{-1}, etc.), etc. were assessed and confirmed to provide editing of target adenosines. In some embodiments, certain nucleobases, sugars and/or internucleotidic linkages provide higher editing levels compared to others. RNA editing was quantified by Sanger sequencing. Additional data are presented in Figure 80 (*e.g.*, oligonucleotides comprising dI, b001A, b002A, b003A, b008U, b008C, Tsm11, Tsm12, b004C, Csm17, etc. at N_{-1}) and Figure 81 (*e.g.*, oligonucleotides comprising dI, Csm11, Csm12, b009Csm11, b009Csm12, etc.). In some embodiments, certain sugars (e.g., natural DNA

sugar) and/or nucleobases (e.g., hypoxanthine, b001A, b003A, etc.) at N_{-1} provide higher editing levels compared to others. In some embodiments, certain sugars (e.g., DNA sugar) and/or nucleobases (e.g., b008U) at N_0 provide higher editing levels compared to others.

[001509] Among other things, the present disclosure provides various internucleotidic linkages for utilization with other structural elements to provide oligonucleotides and compositions thereof. In some embodiments, internucleotidic linkages are non-negatively charged internucleotidic linkages. In some embodiments, internucleotidic linkages are phosphoryl guanidine internucleotidic linkages. As shown in Figure 82, various internucleotidic linkages, e.g., PN internucleotidic linkages such as n001, n004, n008, n025, n026, etc. can be utilized in accordance with the present disclosure in oligonucleotides to provide editing. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various nucleobases (*e.g.*, b008U, hypoxanthine, b014I, etc.), linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001, n004, n008, n025, n026, etc.) internucleotidic linkages) and sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, 2'-MOE modified sugars, etc.) were assessed and confirmed to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. In some embodiments, oligonucleotides comprising various phosphoryl guanidine internucleotidic linkages such as n001, n004, n008, n025, n026, etc. bonded to N_{-1} and N_{-2} provide robust editing. In some embodiments, such internucleotidic linkages are chirally controlled and are *S*p. In some embodiments, one or more of non-n001 phosphoryl guanidine internucleotidic linkages may be independently utilized in place of one or more n001 (and/or one or more other types of linkages).

[001510] As described herein, oligonucleotides may comprise duplex regions or may be utilized as duplexes. In some embodiments, a duplexing oligonucleotide forms a duplex with an oligonucleotide that can target and edit a target adenosine. Certain examples are presented below as examples. Serial dilution concentrations from about 1000 nM to about 0.5 nM. About 5%-20% editing observed at the lowest concentration and about 70%-90% editing observed at the highest concentrations. Primary mouse hepatocytes (huADAR/SA1 Tg) were treated with indicated oligonucleotide compositions targeting SERPINA1-Z allele for 48 hrs (gymnotic). Oligonucleotides comprising various types of nucleobases, linkages (e.g., PS (phosphorothioate), PO (natural phosphate linkage) and/or PN (e.g., phosphoryl guanidine linkages such as n001) internucleotidic linkages) and sugars (e.g., 2'-OMe modified sugars, 2'-F modified sugars, natural DNA sugars, 2'-MOE modified sugars, etc.) can form duplexes with corresponding duplexing oligonucleotides. Certain duplexes were assessed as examples and were confirmed to provide editing of target adenosines. RNA editing was quantified by Sanger sequencing. In some embodiments, certain duplexes provided comparable or increased editing activity relative to a reference. In some embodiments, duplexing oligonucleotide comprise 2'-OR modified sugars (wherein R is not −H, e.g., 2'-OMe modified sugars, 2'-MOE modified sugars, etc.) and/or modified internucleotidic linkages (e.g., phosphorothioate internucleotidic linkage) at both ends. In some embodiments, duplexing oligonucleotides comprise 2'-F modified sugars, 2'-OR modified sugars (wherein R is not −H, e.g.,

2'-OMe modified sugars, 2'-MOE modified sugars, etc.) and/or natural RNA sugars. In some embodiments, it was observed that duplexing oligonucleotide comprising internal natural RNA sugars may provide higher editing efficiency when duplexed with targeting oligonucleotides (e.g., WV-46312).

Oligonucleotides (WV-)	Absolute EC50 (nM)	95% CI (nM)
46312	3.90	2.25 - 5.54
46312/48444	8.92	7.72 - 10.1
46312/48445	5.71	4.89 - 6.52
46312/48446	2.91	2.32 - 3.50
46312/48447	9.68	8.36 - 10.9
46312/48448	6.58	5.83 - 7.33
46312/48449	3.08	2.47 - 3.68
46312/48450	16.66	14.4 - 18.8
46312/48451	8.83	7.92 - 9.73
46312/48452	3.09	2.64 - 3.53

[001511] As described herein, provided technologies can be utilized to edit target adenosines in various nucleic acids. For example, as shown in Figure 83, various oligonucleotides comprising various modifications and patterns thereof can provide editing of target adenosine in UGP2 transcripts. Primary human hepatocytes were treated with indicated oligonucleotide compositions for 48 hrs. RNA editing was quantified by Sanger sequencing. Additional data are presented in Figure 84 as examples. Primary human hepatocytes were treated with indicated oligonucleotide compositions targeting UGP2 at indicated concentrations for 48 hrs. RNA editing was quantified by Sanger sequencing. In some embodiments, oligonucleotides comprising certain structural elements, e.g., 2'-OR modified sugars at end regions, multiple 2'-F blocks separated by multiple separating blocks (e.g., one or more or each independently a 2'-OR block), and/or 2'-F modified sugar at N_{-3}, etc., can provide improved editing efficiency.

[001512] As described herein, provided technologies provide editing *in vivo* and can provide products, e.g., polypeptides, encoded by edited nucleic acids. For example, Figures 85 confirms *in vivo* editing of SERPINA1 and increase of serum AAT levels. Mice transgenic for human ADAR and SERPINA1-Z allele were subcutaneously dosed with PBS or 10mg/kg oligonucleotide on days 0, 2, and 4. Liver biopsies were collected at day 7 and serum AAT was collected pre-dose and day 7. As confirmed in Figures 85, provided oligonucleotide compositions delivered significant editing activity and increased levels of serum AAT relative to reference (*e.g.*, PBS control, pre-dose levels). Serum AAT was quantified using ELISA. Certain additional results are presented in Figure 86, which confirms that various modifications can be utilized in accordance with the present disclosure to provide oligonucleotides that are active *in vivo*. Mice transgenic for human ADAR and SERPINA1-Z allele were subcutaneously dosed with PBS or 10mg/kg oligonucleotides on day 0. Liver biopsies were collected at day 10. Serum was collected pre-dose, day 7, and day 10. Various oligonucleotide compositions were assessed and confirmed to provide editing of target adenosines and

increased levels of serum AAT. RNA editing was quantified by Sanger sequencing. Serum AAT was quantified using ELISA.

[001513] While various embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described in the present disclosure, and each of such variations and/or modifications is deemed to be included. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be example and that the actual parameters, dimensions, materials, and/or configurations may depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments of the present disclosure. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, claimed technologies may be practiced otherwise than as specifically described and claimed. In addition, any combination of two or more features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

CLAIMS

1. An oligonucleotide comprising:

a first domain; and

a second domain,

wherein:

the first domain comprises one or more 2'-F modifications;

the second domain comprises one or more sugars that do not have a 2'-F modification;

about 30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain independently comprise a 2'-F modification; and

30%-70% (e.g., about 30%-60%, 30%-50%, or about 30%, 40%, 50%, 60% or 70%) of sugars in the first domain comprises 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic.

2. The oligonucleotide of claim 1, wherein when the oligonucleotide is contacted with a target nucleic acid comprising a target adenosine in a system, a target adenosine in the target nucleic acid is modified, and the modification is or comprises conversion of the target adenosine to an inosine.

3. The oligonucleotide of claim 2, wherein the first domain comprises one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) 2'-F blocks and one or more (e.g., 1-20, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 2-20, 3-15, 4-15, 5-15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) separating blocks, wherein each sugar in each 2'-F block is independently a 2'-F modified sugar, and wherein each sugar in each separating block is independently a sugar other than a 2'-F modified sugar.

4. The oligonucleotide of claim 3, wherein there are 3 or more 2'-F blocks in the first domain.

5. The oligonucleotide of claim 4, wherein there are 2 or more separating blocks in the first domain.

6. The oligonucleotide of claim 5, wherein each sugar in a separating block is independently a 2'-OR modified sugar wherein R is optionally substituted C_{1-6} aliphatic.

7. The oligonucleotide of claim 5, wherein each block in a first domain that is bonded to a 2'-F block in a first domain is a separating block.

8. An oligonucleotide comprising:

a first domain; and

a second domain,

wherein:

the first domain comprises one or more 2'-F modifications;

the second domain comprises one or more sugars that do not have a 2'-F modification.

9. An oligonucleotide comprising one or more modified sugars and/or one or more modified internucleotidic linkages, wherein the oligonucleotide comprises a first domain and a second domain each independently comprising one or more nucleobases.

10. The oligonucleotide of claim 8 or 9, wherein when the oligonucleotide is contacted with a target

nucleic acid comprising a target adenosine in a system, a target adenosine in the target nucleic acid is modified, and the modification is or comprises conversion of the target adenosine to an inosine.

11. The oligonucleotide of claim 7, wherein the oligonucleotide has a length of about 26-35 nucleobases.

12. The oligonucleotide of claim 7, wherein the each of the first and second domain independently has a length of about 10-50 nucleobases.

13. The oligonucleotide of claim 12, wherein about 50%-100% of internucleotidic linkages in the first domain are modified internucleotidic linkages.

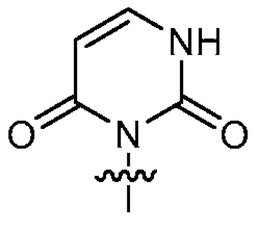
14. The oligonucleotide of claim 13, wherein the second domain comprise a nucleoside opposite to a target adenosine when the oligonucleotide is aligned with a target nucleic acid for complementarity.

15. The oligonucleotide of claim 14, wherein the opposite nucleobase is optionally substituted or protected U, or is an optionally substituted or protected tautomer of U, or is optionally substituted or protected C, or is an optionally substituted or protected tautomer of C, or is optionally substituted or protected A, or is an optionally substituted or protected tautomer of A, or is optionally substituted or protected nucleobase of pseudoisocytosine, or is an optionally substituted or protected tautomer of the nucleobase of pseudoisocytosine, or is a nucleobase BA, wherein BA is or comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 hetereoatoms.

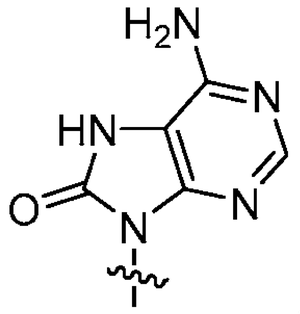
16. The oligonucleotide of claim 15, wherein the nucleobase is BA, wherein BA is or comprises Ring BA or a tautomer thereof, wherein Ring BA is an optionally substituted, 5-20 membered, monocyclic, bicyclic or polycyclic ring having 0-10 hetereoatoms.

17. The oligonucleotide of claim 16, wherein BA has weaker hydrogen bonding with the target adenine of the adenosine compared to U.

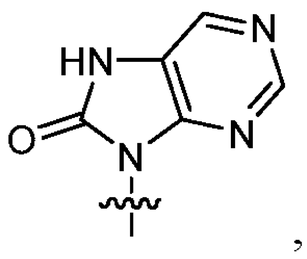
18. The oligonucleotide of claim 16, wherein Ring BA comprises $===X^2===X^3===$, $===X^2===X^3===X^4===$, $-X^1(===)===X^2===X^3===$, $-X^1(===)===X^2===X^3===X^4===$, or has the structure of formula BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a or BA-III-b.

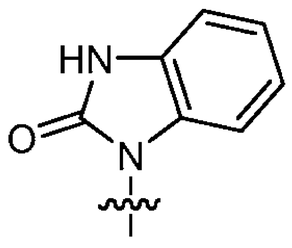
19. The oligonucleotide of claim 14, wherein the opposite nucleobase is 

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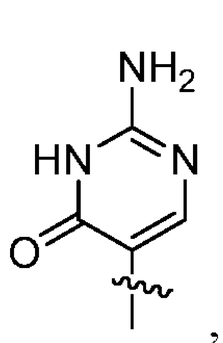
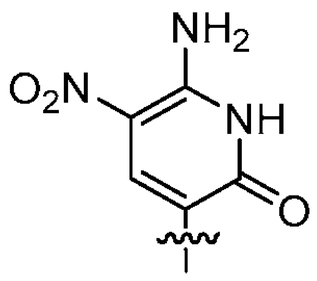
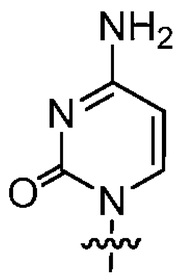
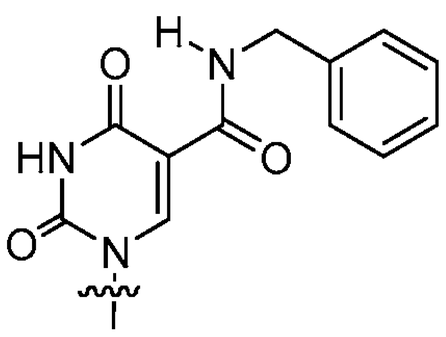
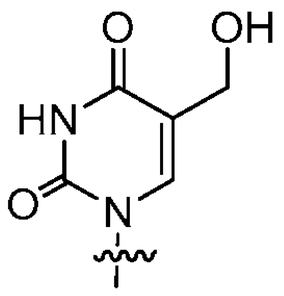
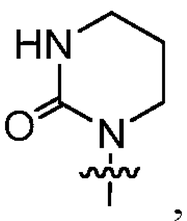
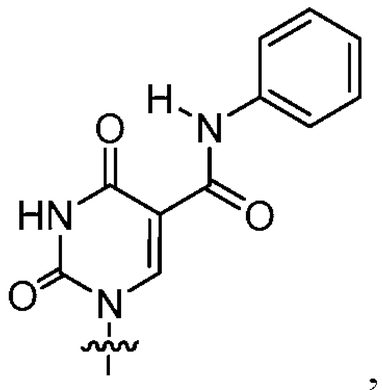
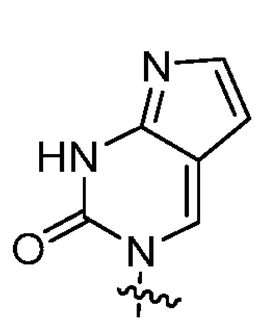
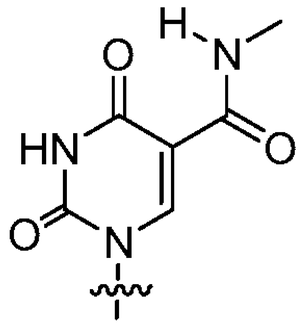
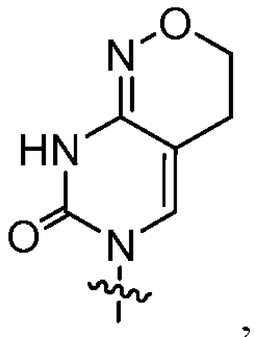
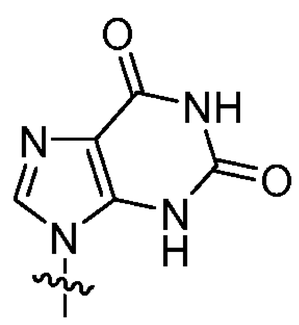
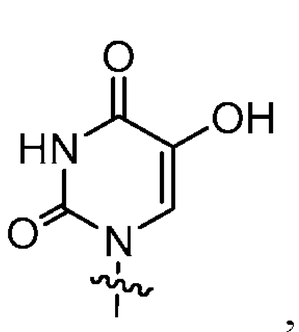
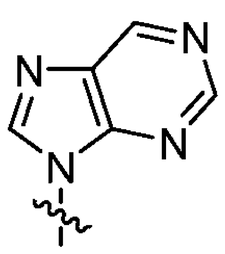
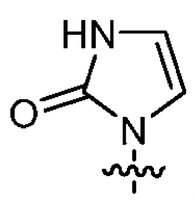
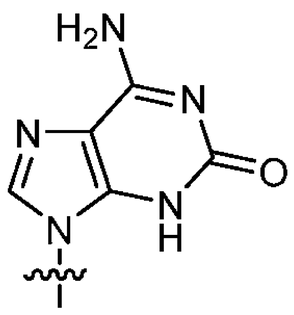
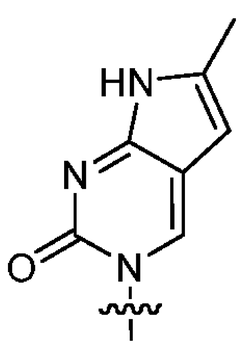
20. The oligonucleotide of claim 14, wherein the opposite nucleobase is 

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21. The oligonucleotide of claim 14, wherein the opposite nucleobase is 

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22. The oligonucleotide of claim 14, wherein about 50%-100% of sugars in the second domain are independently modified sugars with a modification that is not 2'-F.

23. The oligonucleotide of claim 22, wherein about 50%-100% of internucleotidic linkages in the second domain are modified internucleotidic linkages.

24. The oligonucleotide of claim 23, wherein each modified internucleotidic linkages is independently a phosphorothioate internucleotidic linkage or a non-negatively charged internucleotidic linkage.

25. The oligonucleotide of claim 24, wherein the second domain comprises one or more phosphorothioate internucleotidic linkages.

26. The oligonucleotide of claim 25, wherein the second domain comprises 1, 2, 3, 4, or 5 non-negatively charged internucleotidic linkages.

27. The oligonucleotide of claim 26, wherein the internucleotidic linkage between the last and the second last nucleosides of the second domain is a non-negatively charged internucleotidic linkage.

28. The oligonucleotide of claim 25, wherein at least 50%-100% of chiral internucleotidic linkages in the second domain is chirally controlled.

29. The oligonucleotide of claim 28, wherein the second domain comprises or consists of from the 5' to 3' a first subdomain, a second subdomain , and a third subdomain.

30. The oligonucleotide of claim 29, wherein the first subdomain has a length of about 5-50 nucleobases.

31. The oligonucleotide of claim 30, wherein about 50%-100% of sugars in the first subdomain are independently modified sugars with a modification that is not 2'-F.

32. The oligonucleotide of claim 31, wherein the second subdomain has a length of 3 nucleobases.

33. The oligonucleotide of claim 32, wherein the second subdomain comprises a nucleoside opposite to a

target adenosine.

34. The oligonucleotide of claim 33, wherein the second subdomain comprises one or more natural DNA sugars.

35. The oligonucleotide of claim 34, wherein the second subdomain comprises one or more natural RNA sugars.

36. The oligonucleotide of claim 34, wherein the second subdomain comprises about a 2'-F modified sugars.

37. The oligonucleotide of claim 34, wherein the sugar of the opposite nucleoside comprises a 2'-OH.

38. The oligonucleotide of claim 34, wherein the sugar of the opposite nucleoside is a natural DNA sugar.

39. The oligonucleotide of claim 34, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-...N_1N_0...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

40. The oligonucleotide of claim 34, wherein the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-...N_1N_0...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) comprises 2'-F.

41. The oligonucleotide of claim 34, wherein the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-...N_0N_{-1}...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

42. The oligonucleotide of claim 34, wherein each of the sugar of the opposite nucleoside, the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-...N_1N_0...3', wherein when aligned with a target, N_0 is opposite to a target adenosine), and the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-...N_0N_{-1}...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is independently a natural DNA sugar.

43. The oligonucleotide of claim 34, wherein the sugar of the opposite nucleoside is a natural DNA sugar, the sugar of a nucleoside 5'-next to the opposite nucleoside (sugar of N_1 in 5'-...N_1N_0...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a 2'-F modified sugar, and the sugar of a nucleoside 3'-next to the opposite nucleoside (sugar of N_{-1} in 5'-...N_0N_{-1}...3', wherein when aligned with a target, N_0 is opposite to a target adenosine) is a natural DNA sugar.

44. The oligonucleotide of claim 34, wherein the nucleoside opposite to a target nucleoside is connected to its 3' immediate nucleoside through a *R*p phosphorothioate internucleotidic linkage.

45. The oligonucleotide of claim 34, wherein the nucleoside (position -1) that is 3' immediate to an nucleoside opposite to a target nucleoside (position 0) is connected to its 3' immediate nucleoside (position -2) through a non-negatively charged internucleotidic linkage.

46. The oligonucleotide of claim 34, wherein the 3'-immediate nucleoside comprises a base that is not G.

47. The oligonucleotide of claim 34, wherein the 3'-immediate nucleoside comprises hypoxanthine.

48. The oligonucleotide of claim 34, wherein the third subdomain has a length of about 1-10 nucleobases.

49. The oligonucleotide of claim 34, wherein the oligonucleotide comprises a moiety that is or comprises GalNAc or a derivative thereof.

50. An oligonucleotide comprising a modified nucleobase or a modified linkage as described herein.

51. An oligonucleotide, wherein the oligonucleotide is otherwise identical to an oligonucleotide of any one of the preceding claims, except that at a position of a modified internucleotidic linkage is a linkage having the structure of $-O^5-P^L(R^{CA})-O^3-$, wherein:

P^L is P, or P(=W);

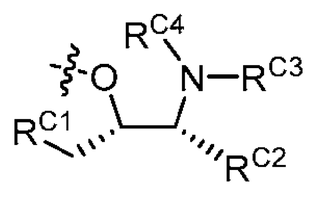
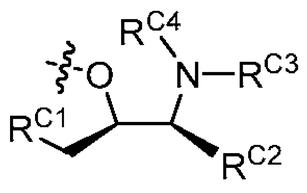
W is O, S, or W^N;

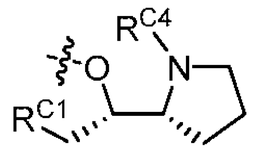
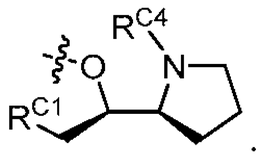
R^{CA} is or comprises an optionally substituted or capped chiral auxiliary moiety,

O^5 is an oxygen bonded to a 5'-carbon of a sugar, and

O^3 is an oxygen bonded to a 3'-carbon of a sugar.

52. The oligonucleotide of claim 51, wherein at each position of a modified internucleotidic linkage is independently a linkage having the structure of $-O^5-P^L(W)(R^{CA})-O^3-$.

53. The oligonucleotide of claim 52, wherein each R^{CA} is independently  or  , wherein R^{C1} is R, $-Si(R)_3$ or $-SO_2R$, R^{C2} and R^{C3} are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having, in addition to the nitrogen atom, 0-2 heteroatoms, R^{C4} is $-H$ or $-C(O)R'$.

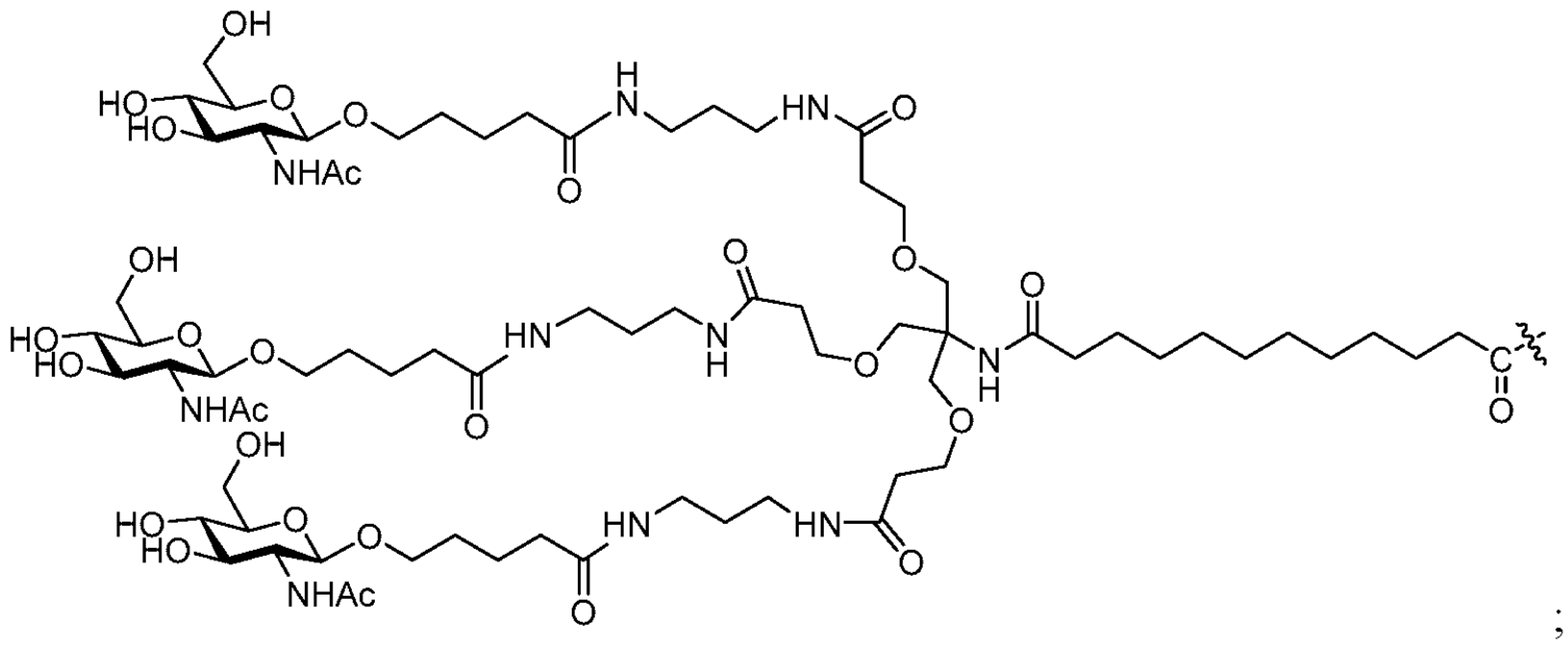
54. The oligonucleotide of claim 52, wherein each R^{CA} is independently  or  .

55. The oligonucleotide of claim 54, wherein R^{C1} is $-SiPh_2Me$, or wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted phenyl.

56. The oligonucleotide of any one of the preceding claims, wherein the base sequence of the oligonucleotide is or comprises a sequence that differs at no more than 1, 2, 3, 4, or 5 positions from UUCAGUCCCUUUCTCIUCGA, CCCCAGCAGCUUCAGUCCCUUUCTCGUCGA, or CCCAGCAGCUUCAGUCCCUUUCTUIUCGAU, wherein each U can be independently replaced with T and vice versa.

57. An oligonucleotide having the structure of

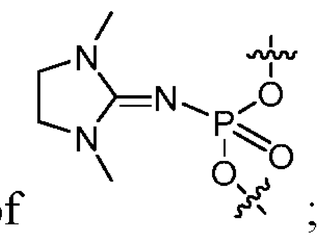
Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein:



Mod001 is ;

L001 is −NH−$(CH_2)_6$−, wherein −NH− is connected to Mod001;

m represents a 2'-OMe modification to a nucleoside;

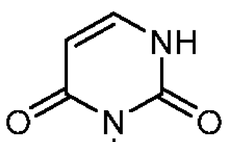


n001R represents a *R*p n001 linkage, wherein a n001 linkage has the structure of ;

n001S represents a *S*p n001 linkage;

*S represents a *S*p phosphorothioate linkage;

f represents a 2'-F modification to a nucleoside;



b008U represents a nucleoside whose base is ; and

I represents a nucleoside whose base is hypoxanthine.

58. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 or the specification.

59. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SmCfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

60. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SmCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

61. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SmCfC*SfUn001RfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are

as described in claim 1496 (and/or the specification).

62. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SfU*SfUn001RfC*SfAfGn001RfUmCmCfC*SfU*SmUmU*SfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

63. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SfCmA*SfG*SfCmU*SfUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfU*SfU*SmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

64. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

65. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*SmCmAfG*SfC*SmUfUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RmUmUfC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

66. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUmC*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

67. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SmGn001RfUm5Ceo*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

68. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUmCmC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

69. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SmCTeo*SmUn001RmCfA*SfGn001RmUm5CeomC*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

70. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*Sm5CeoTeo*SmUn001Rm5CeofA*SfGn001RmUm5Ceom5Ceo*SfC*SfU*STeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein

modifications are as described in claim 1496 (and/or the specification).

71. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*SmUmUn001RmCfA*SfGn001RfUm5Ceo*SfC*SmCmUn001RmUTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

72. An oligonucleotide having the structure of Mod001L001mCn001RmC*SmC*SfA*SfG*Sm5CeoAeofG*SfC*STeofUn001RmCfA*SfGn001RfUm5Ceo*SfC*SfC*SfUn001RTeoTeofC*ST*Sb008U*SIn001SmUfC*SmG*SmAn001RmU, wherein modifications are as described in claim 1496 (and/or the specification).

73. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide is in a salt form.

74. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide is in a pharmaceutically acceptable salt form.

75. The oligonucleotide of any one of the preceding claims, wherein diastereomeric excess of each chiral linkage phosphorus is independently about or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%.

76. The oligonucleotide of any one of claims 1-75, wherein the oligonucleotide has a purity of about 10%-100%.

77. A pharmaceutical composition which comprises or delivers an effective amount of an oligonucleotide of any one of claims 1-76 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

78. An oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more chiral internucleotidic linkages (“chirally controlled internucleotidic linkages”);

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of claims 1-76 or an acid, base, or salt form thereof; or

an oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more chiral internucleotidic linkages (“chirally controlled internucleotidic linkages”);

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of claims 1-76 or an acid, base, or salt form thereof; or

a composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality; and

wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of claims 1-76 or an acid, base, or salt form thereof; or

an oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine; or

an oligonucleotide composition comprising one or more pluralities of oligonucleotides, wherein oligonucleotides of each plurality independently share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the common base sequence of each plurality is independently complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine; or

a composition comprising a plurality of oligonucleotides which are of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

d) a common pattern of backbone phosphorus modifications;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, pattern of backbone linkages and pattern of backbone phosphorus modifications, for oligonucleotides of the particular oligonucleotide type, or a non-random level of all oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality; and

wherein the common base sequence is complementary to a base sequence of a portion of a nucleic acid which portion comprises a target adenosine.

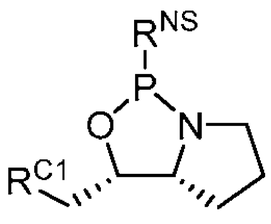
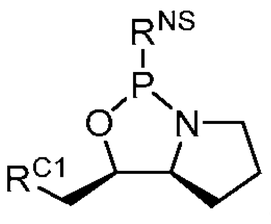
79. The composition of claim 78, wherein each oligonucleotide of the plurality is independently an oligonucleotide of any one of claims 57-72 or a pharmaceutically acceptable salt thereof.

80. The composition of any one of claims 78-79, wherein the level of oligonucleotides of a plurality in oligonucleotides in the composition that share the common base sequence of the plurality is about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages, or wherein the level of oligonucleotides of a plurality in oligonucleotides in the composition that share the same constitution as an oligonucleotide of the plurality or a salt thereof is about or at least about $(DS)^{nc}$, wherein DS is about 85%-100% (e.g., about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages

81. A phosphoramidite, wherein the nucleobase of the phosphoramidite is a nucleobase as described herein or a tautomer thereof, wherein the nucleobase or tautomer thereof is optionally substituted or protected, or

a phosphoramidite, wherein the nucleobase is or comprises Ring BA, wherein Ring BA has the structure of BA-I, BA-I-a, BA-I-b, BA-II, BA-II-a, BA-II-b, BA-III, BA-III-a, BA-III-b, BA-IV, BA-IV-a, BA-IV-b, BA-V, BA-V-a, BA-V-b, or BA-VI, or a tautomer of Ring BA, wherein the nucleobase is optionally substituted or protected.

82. The phosphoramidite of claim 81, wherein the phosphoramidite has the structure of R^{NS}–$P(OR)N(R)_2$, wherein R^{NS} is a optionally protected nucleoside moiety, and each R is as described herein, preferably wherein phosphoramidite has the structure of R^{NS}–$P(OCH_2CH_2CN)N(i\text{-}Pr)_2$.

83. The phosphoramidite of claim 81, wherein the phosphoramidite comprises a chiral auxiliary moiety, wherein the phosphorus is bonded to an oxygen and a nitrogen atom of the chiral auxiliary moiety, preferably wherein the phosphoramidite has the structure of  or  .

84. The phosphoramidite of claim 83, wherein R^{C1} is $-SiPh_2Me$.

85. The phosphoramidite of claim 83, wherein R^{C1} is $-SO_2R$, wherein R is optionally substituted $C_{1\text{-}10}$ aliphatic or wherein R is optionally substituted phenyl.

86. A method for preparing an oligonucleotide or composition, comprising coupling a 5'-OH of an oligonucleotide or a nucleoside with a phosphoramidite of any one of claims 81-85.

87. A method for characterizing an oligonucleotide or a composition, comprising:

administering the oligonucleotide or composition to a cell or a population thereof comprising or

expressing an ADAR1 polypeptide or a characteristic portion thereof, or a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof; or

administering the oligonucleotide or composition to a non-human animal or a population thereof comprising or expressing an ADAR1 polypeptide or a characteristic portion thereof, or a polynucleotide encoding an ADAR1 polypeptide or a characteristic portion thereof.

88. A method for modifying a target adenosine in a target nucleic acid, comprising contacting the target nucleic acid with an oligonucleotide or composition of any one of the preceding claims; or

a method for deaminating a target adenosine in a target nucleic acid, comprising contacting the target nucleic acid with an oligonucleotide or composition of any one of the preceding claims; or

a method for producing, or restoring or increasing level of a product of a particular nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition of any one of the preceding claims, wherein the target nucleic acid comprises a target adenosine, and the particular nucleic acid differs from the target nucleic acid in that the particular nucleic acid has an I or G instead of the target adenosine; or

a method for reducing level of a product of a target nucleic acid, comprising contacting a target nucleic acid with an oligonucleotide or composition of any one of the preceding claims, wherein the target nucleic acid comprises a target adenosine; or

a method, comprising:

contacting an oligonucleotide or composition of any one of the preceding claims with a sample comprising a target nucleic acid and an adenosine deaminase, wherein:

the base sequence of the oligonucleotide or oligonucleotides in the oligonucleotide composition is substantially complementary to that of the target nucleic acid; and

the target nucleic acid comprises a target adenosine;

wherein the target adenosine is modified; or

a method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition; or

a method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chiral internucleotidic linkages than oligonucleotides of the reference plurality; or

a method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality; and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition; or

a method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise more sugars with 2'-F modification, more sugars with 2'-OR modification wherein R is not −H, and/or more chirally controlled chiral internucleotidic linkages than oligonucleotides of the reference plurality; or

a method, comprising

1) obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

2) obtaining a reference level of modification of a target adenosine in a target nucleic acid, which level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition); and

the first oligonucleotide composition provides a higher level of modification compared to oligonucleotides of the reference oligonucleotide composition; or

a method, comprising

obtaining a first level of modification of a target adenosine in a target nucleic acid, which level is observed when a first oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the first oligonucleotide composition comprises a first plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid; and

wherein the first level of modification of a target adenosine is higher than a reference level of modification of the target adenosine, wherein the reference level is observed when a reference oligonucleotide composition is contacted with a sample comprising the target nucleic acid and an adenosine deaminase, wherein the reference oligonucleotide composition comprises a reference plurality of oligonucleotides sharing the same base sequence which is substantially complementary to that of the target nucleic acid;

wherein:

oligonucleotides of the first plurality comprise one or more chirally controlled chiral internucleotidic linkages; and

oligonucleotides of the reference plurality comprise no chirally controlled chiral internucleotidic linkages (a reference oligonucleotide composition is a "stereorandom composition).

89. The method of claim 88, wherein a first oligonucleotide composition is an oligonucleotide composition of any one of the preceding claims.

90. The method of any one of claims 86-88, wherein the deaminase is an ADAR enzyme.

91. The method of any one of claims 87-90, wherein the target nucleic acid is more associated with a condition, disorder or disease, or decrease of a desired property or function, or increase of an undesired property or function, compared to a nucleic acid which differs from the target nucleic acid in that it has an I or G at the position of the target adenosine instead of the target adenosine.

92. The method of claim 91, wherein the target adenosine is a G to A mutation.

93. A method for preventing or treating a condition, disorder or disease, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding claims; or

a method for preventing or treating a condition, disorder or disease associated with a G to A mutation, comprising administering or delivering to a subject susceptible thereto or suffering therefrom an effective amount of an oligonucleotide or composition of any one of the preceding claims.

94. The method of claim 93, wherein the condition, disorder or disease is amenable to an A to G or A to I modification.

95. A compound, oligonucleotide, composition or method of the specification or any one of Example Embodiments 1-1905.

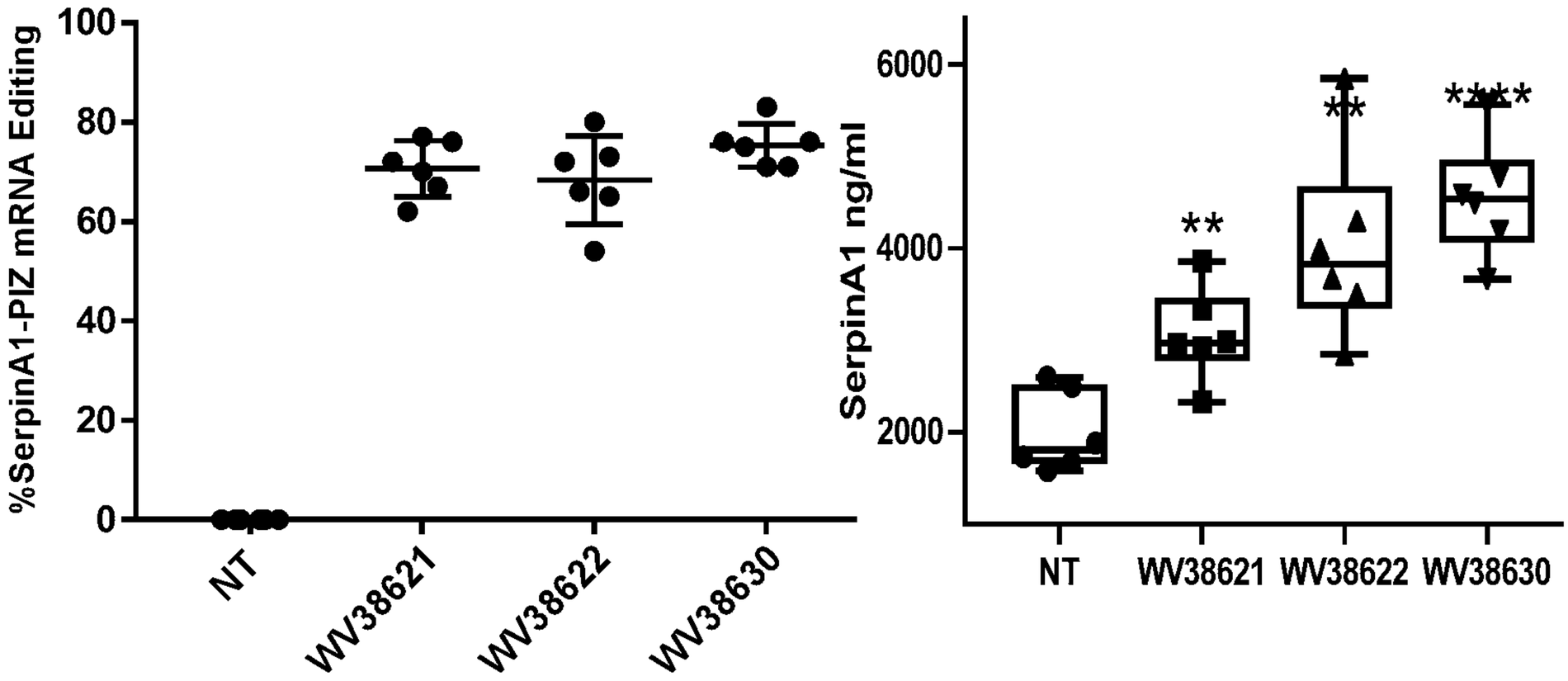
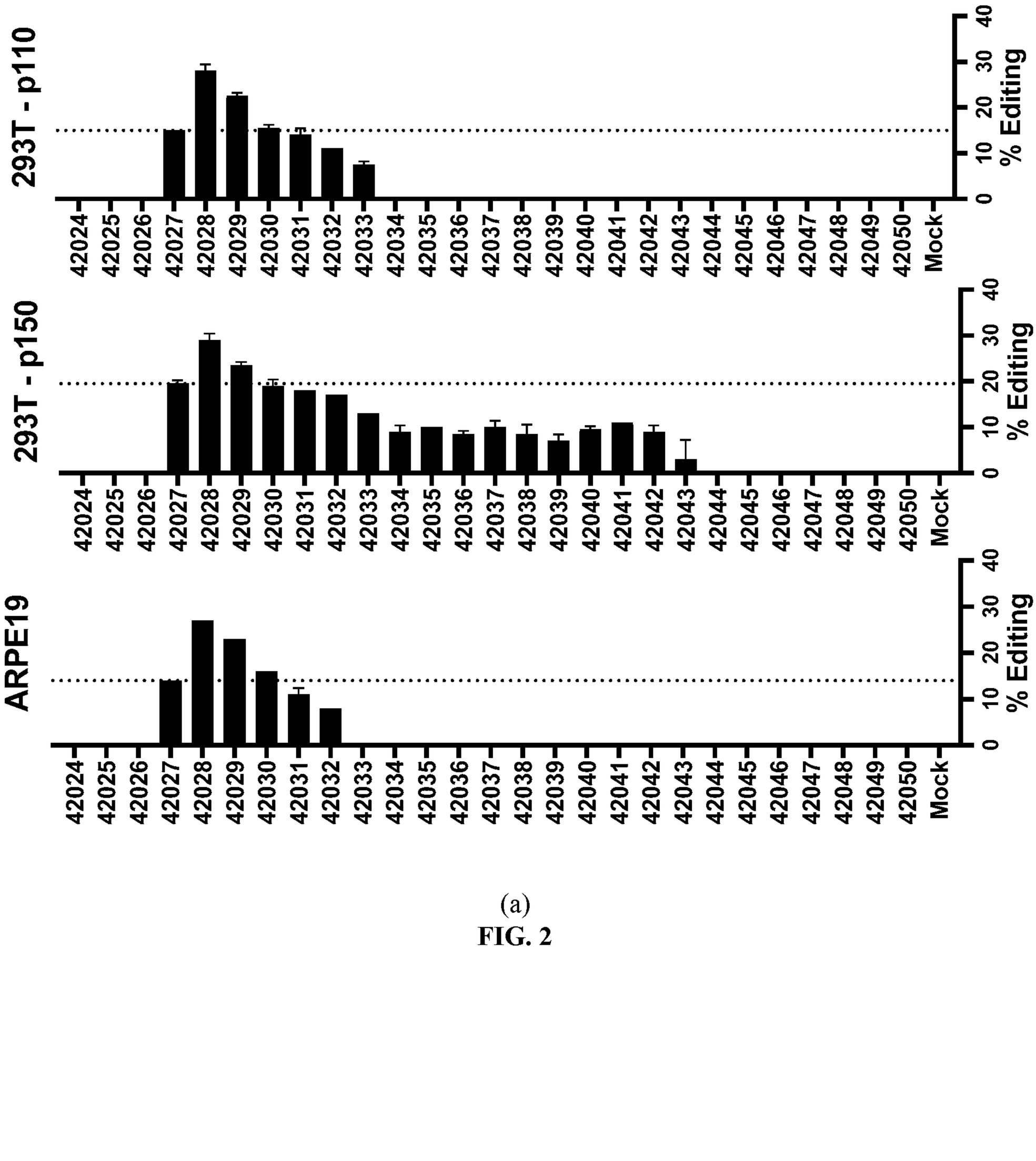
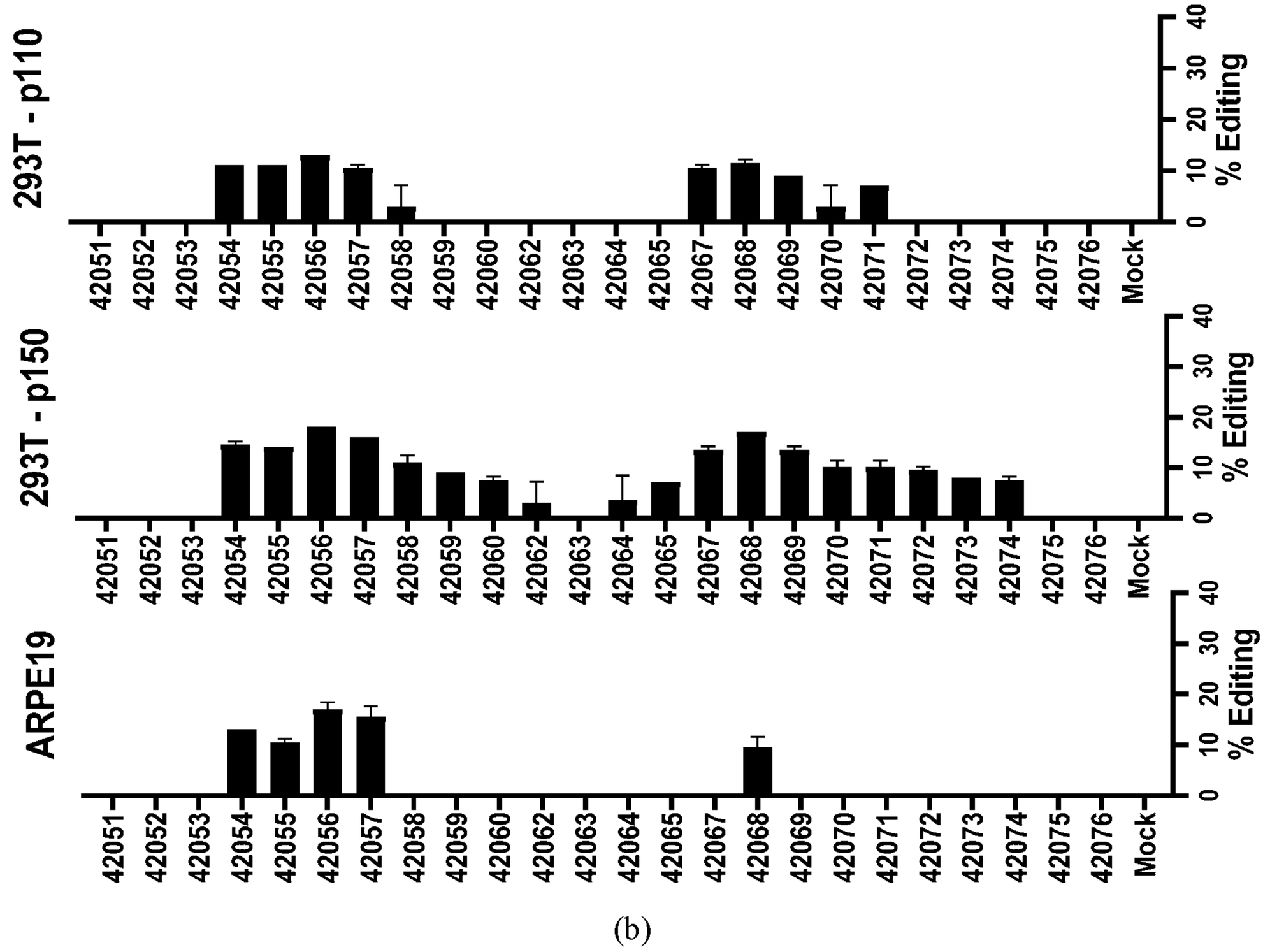

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100
80
60
40
20
0
NT
WV38621
WV38622
WV38630
SerpinA1 ng/ml
6000
4000
2000
**
**
****
NT
WV38621
WV38622
WV38630

FIG. 1


293T - p110
293T - p150
ARPE19
% Editing
0
10
20
30
40
42024
42025
42026
42027
42028
42029
42030
42031
42032
42033
42034
42035
42036
42037
42038
42039
42040
42041
42042
42043
42044
42045
42046
42047
42048
42049
42050
Mock

(a)

FIG. 2


293T - p110
293T - p150
ARPE19
% Editing
0
10
20
30
40
42051
42052
42053
42054
42055
42056
42057
42058
42059
42060
42062
42063
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42069
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42071
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42074
42075
42076
Mock

(b)

FIG. 2

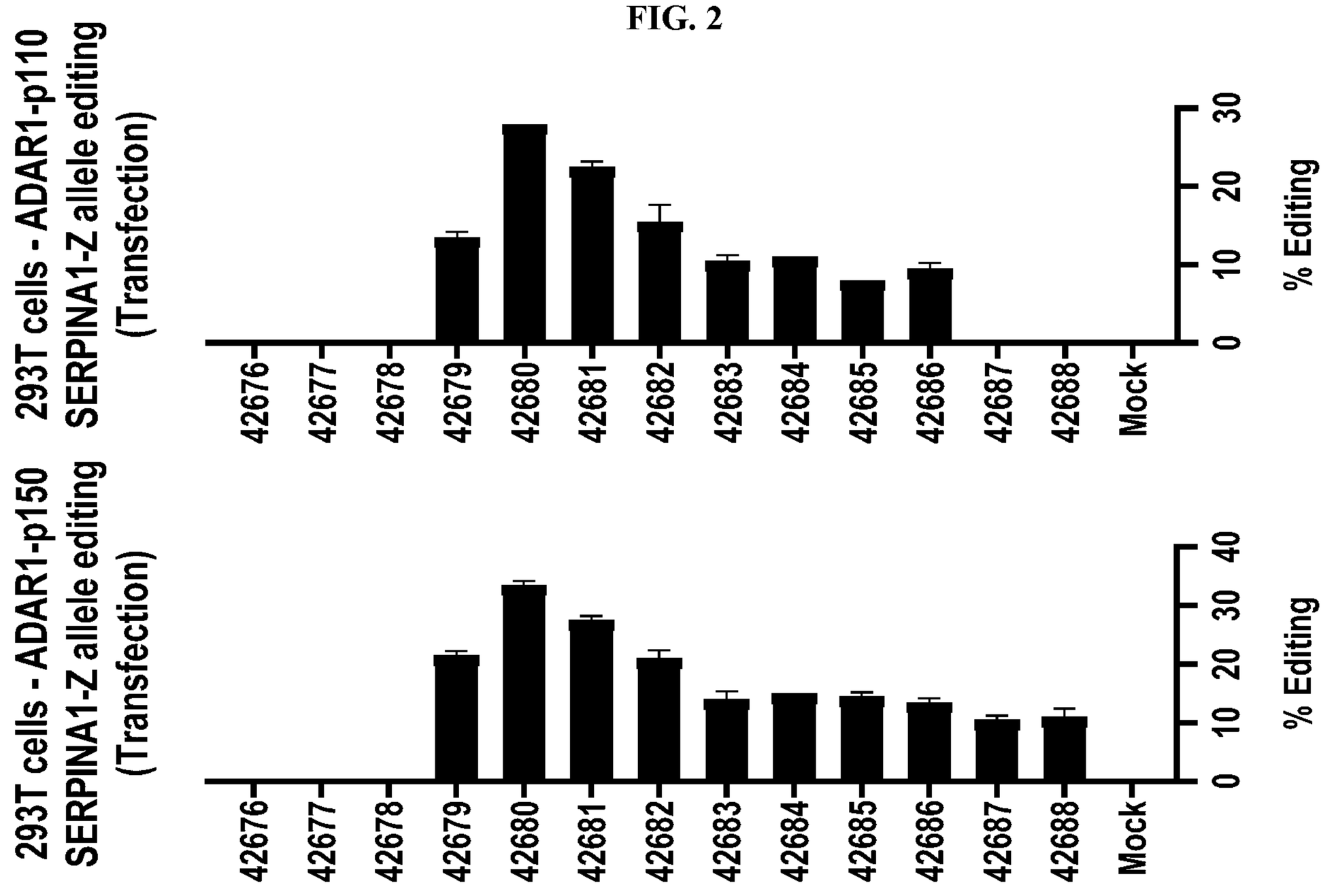

293T cells - ADAR1-p110
SERPINA1-Z allele editing
(Transfection)
293T cells - ADAR1-p150
SERPINA1-Z allele editing
(Transfection)
% Editing
0
10
20
30
40
42676
42677
42678
42679
42680
42681
42682
42683
42684
42685
42686
42687
42688
Mock

FIG. 3

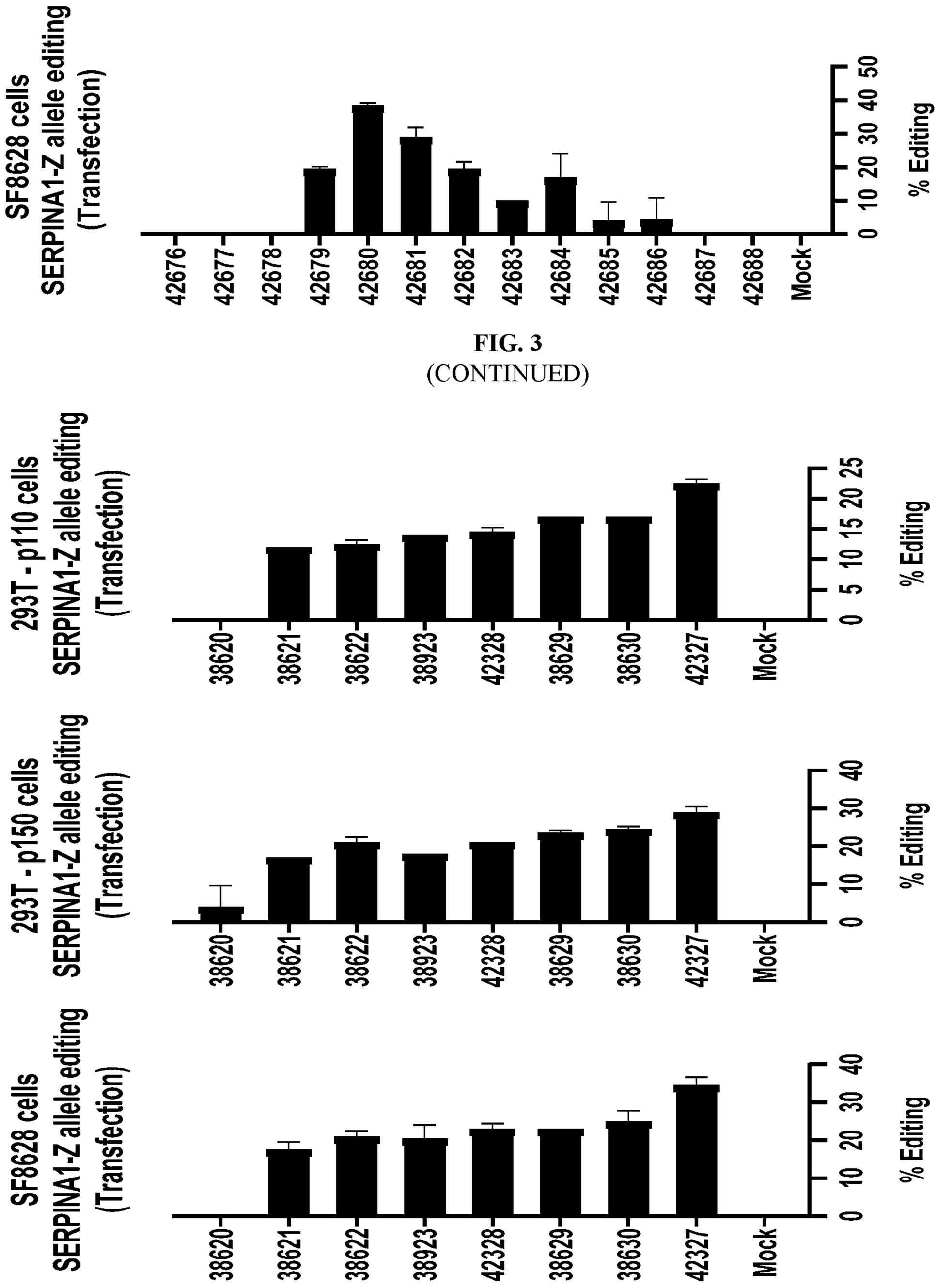


FIG. 3
(CONTINUED)

FIG. 4

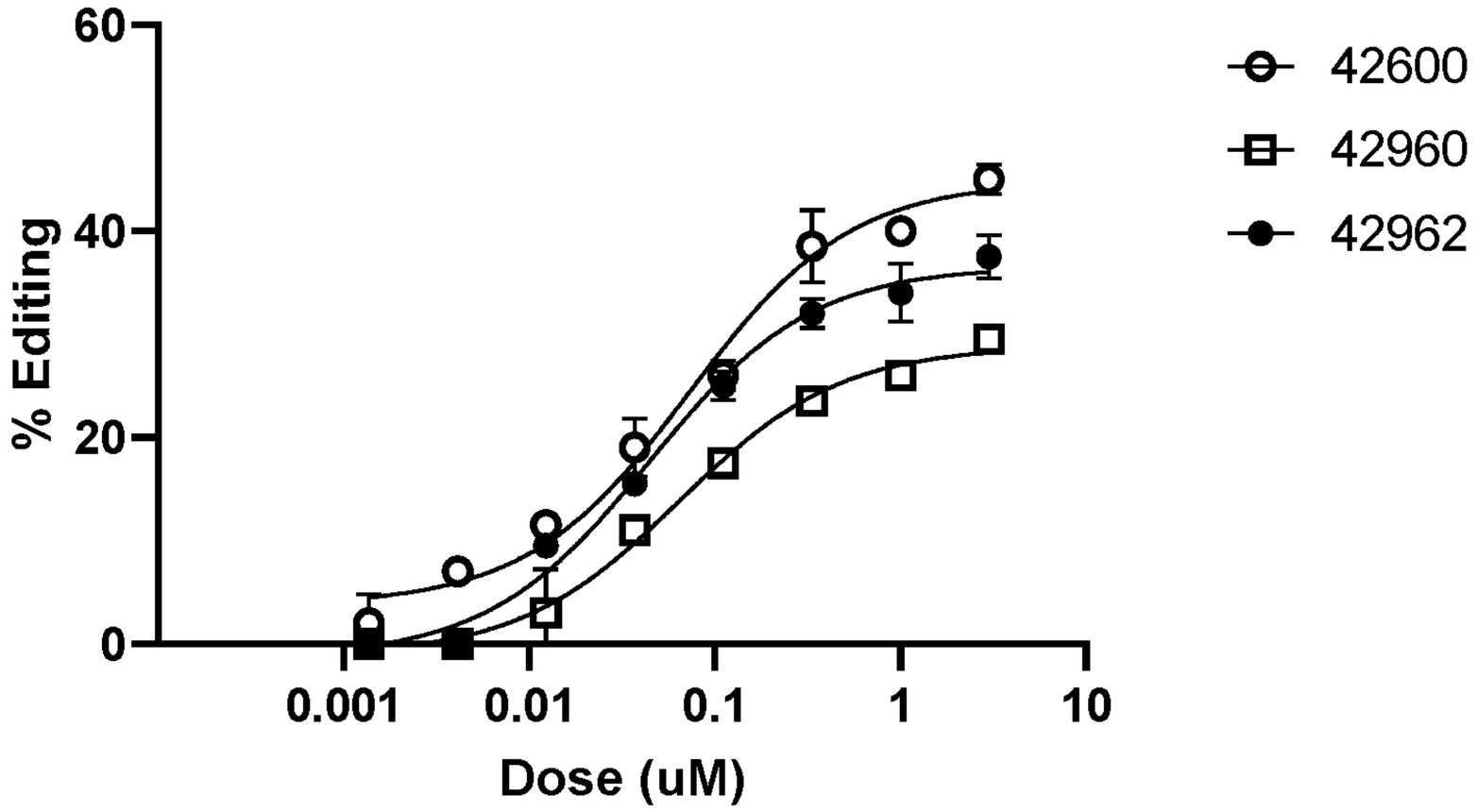


FIG. 5

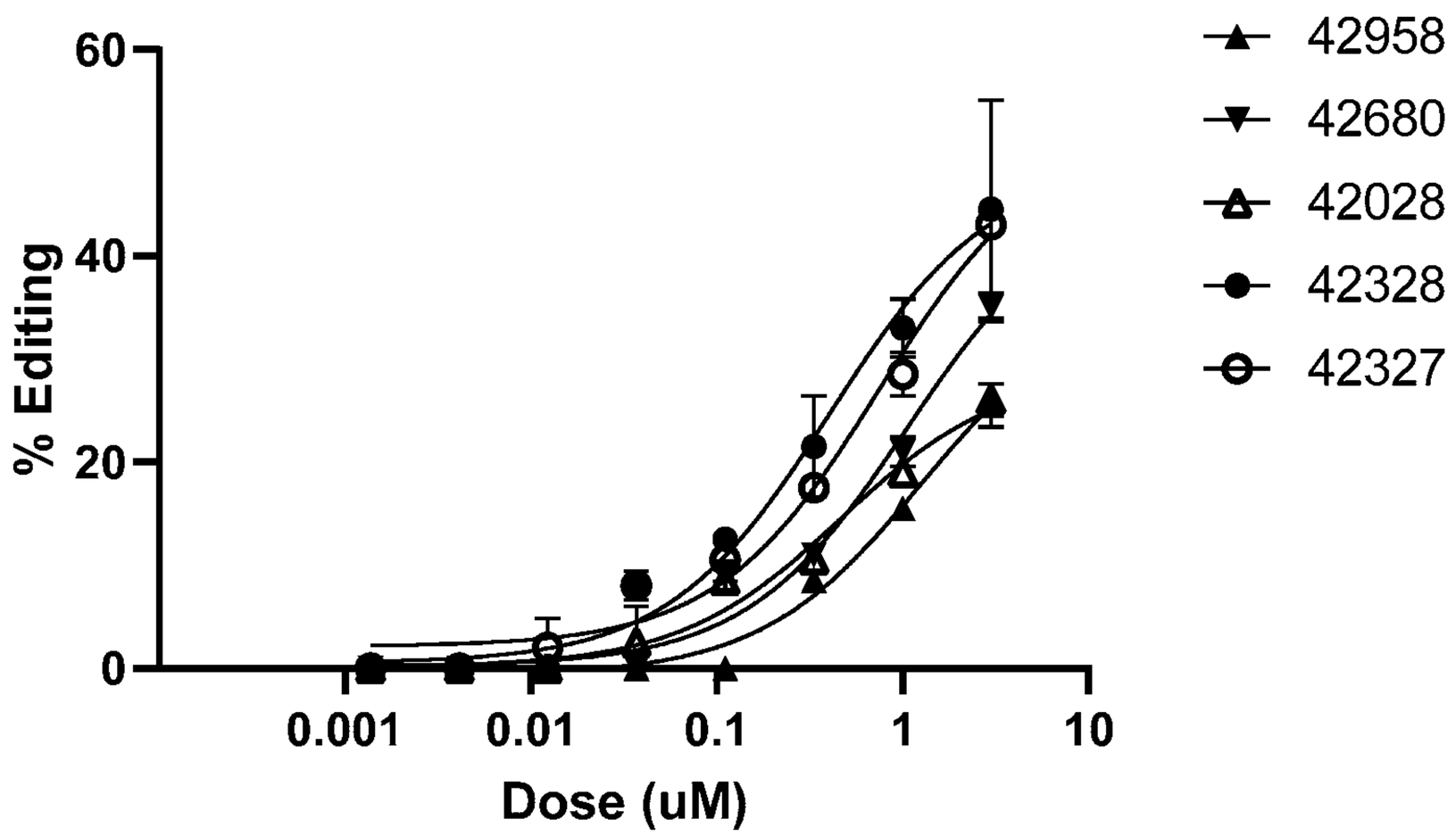


FIG. 6

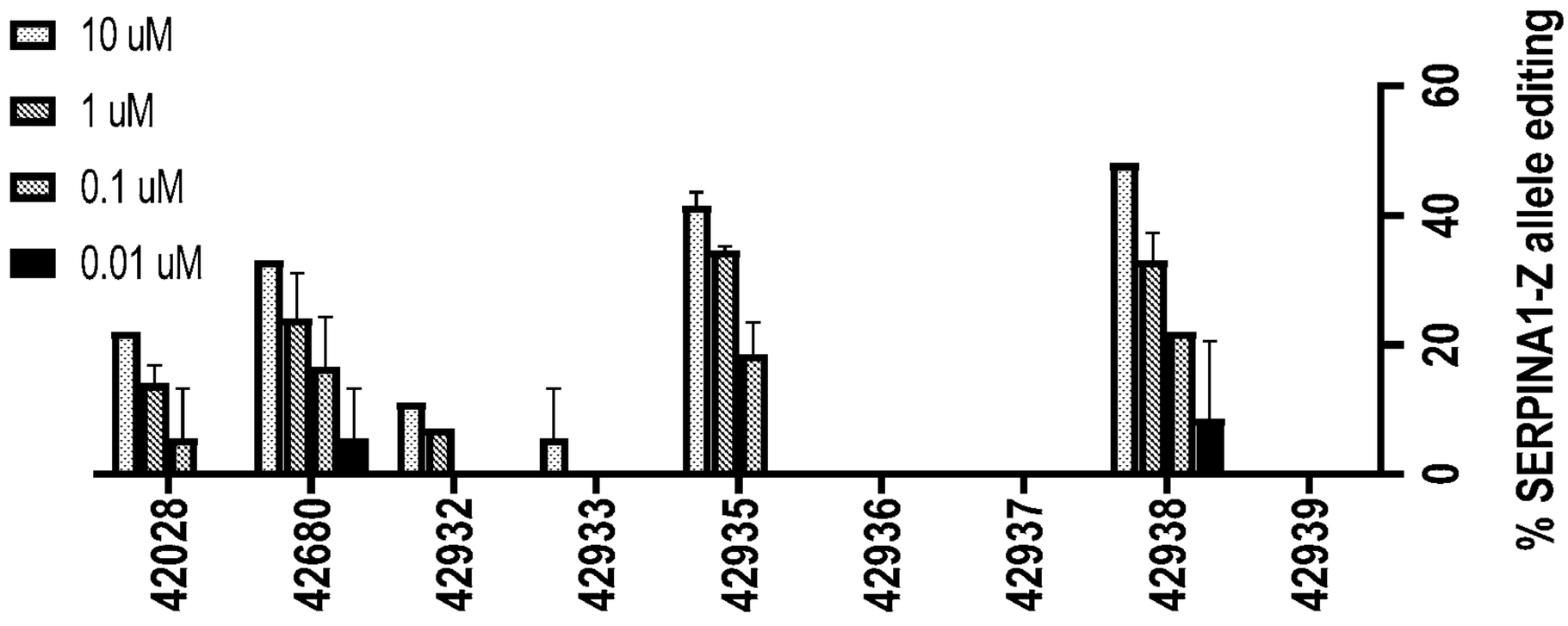


FIG. 7

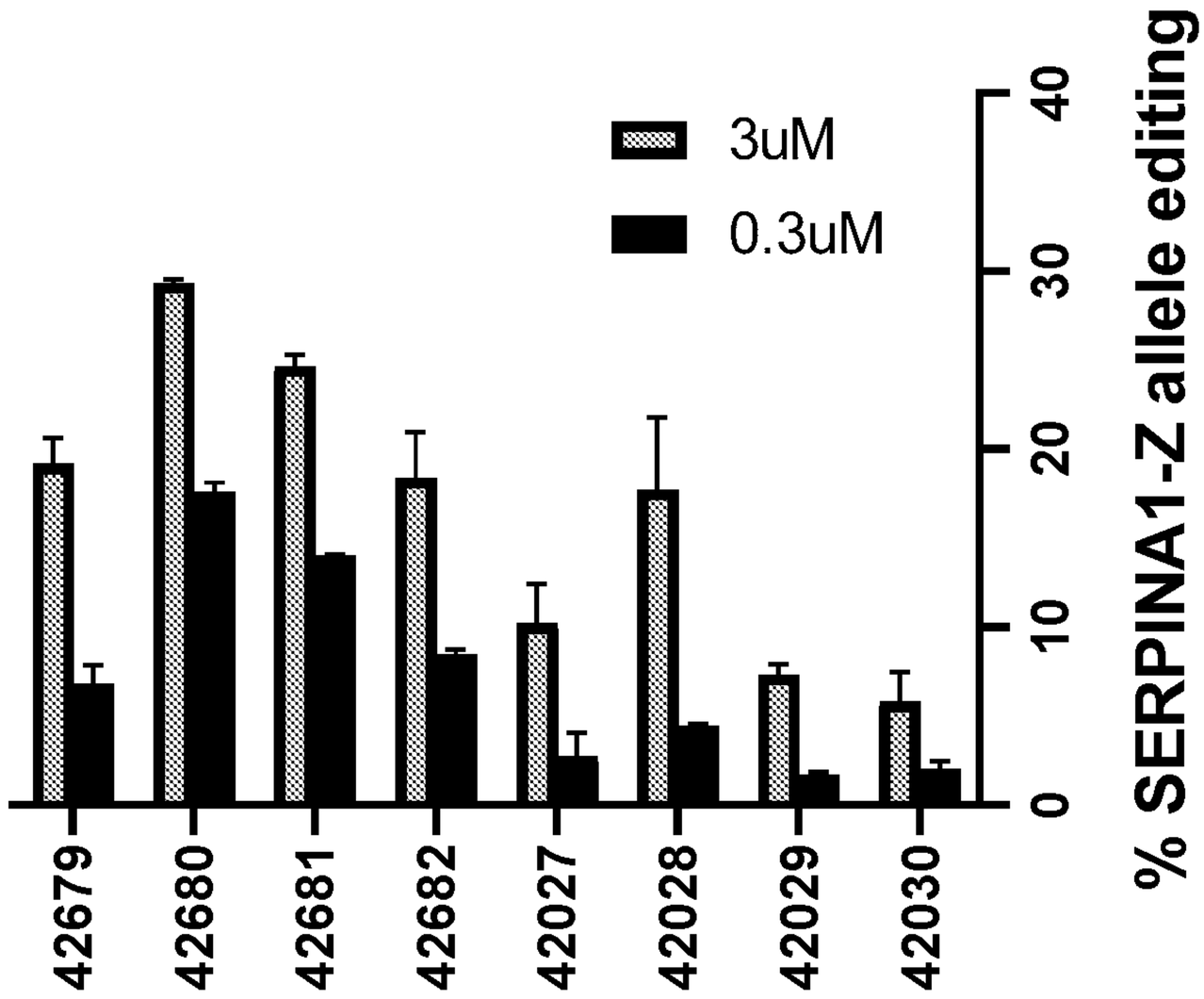

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0.3uM
% SERPINA1-Z allele editing
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20
30
40
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42680
42681
42682
42027
42028
42029
42030

FIG. 8

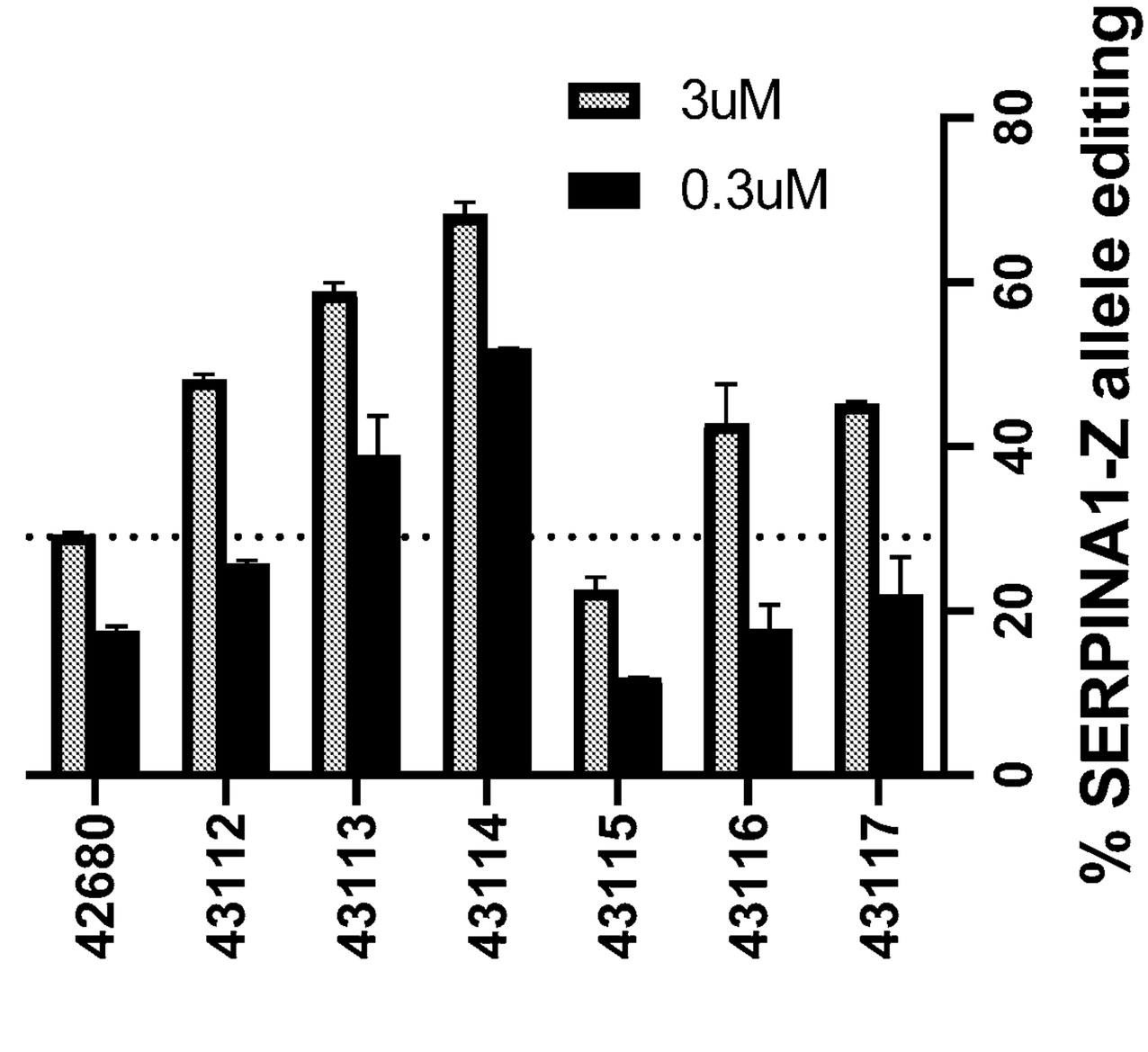

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0.3uM
% SERPINA1-Z allele editing
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80
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43114
43115
43116
43117

FIG. 9

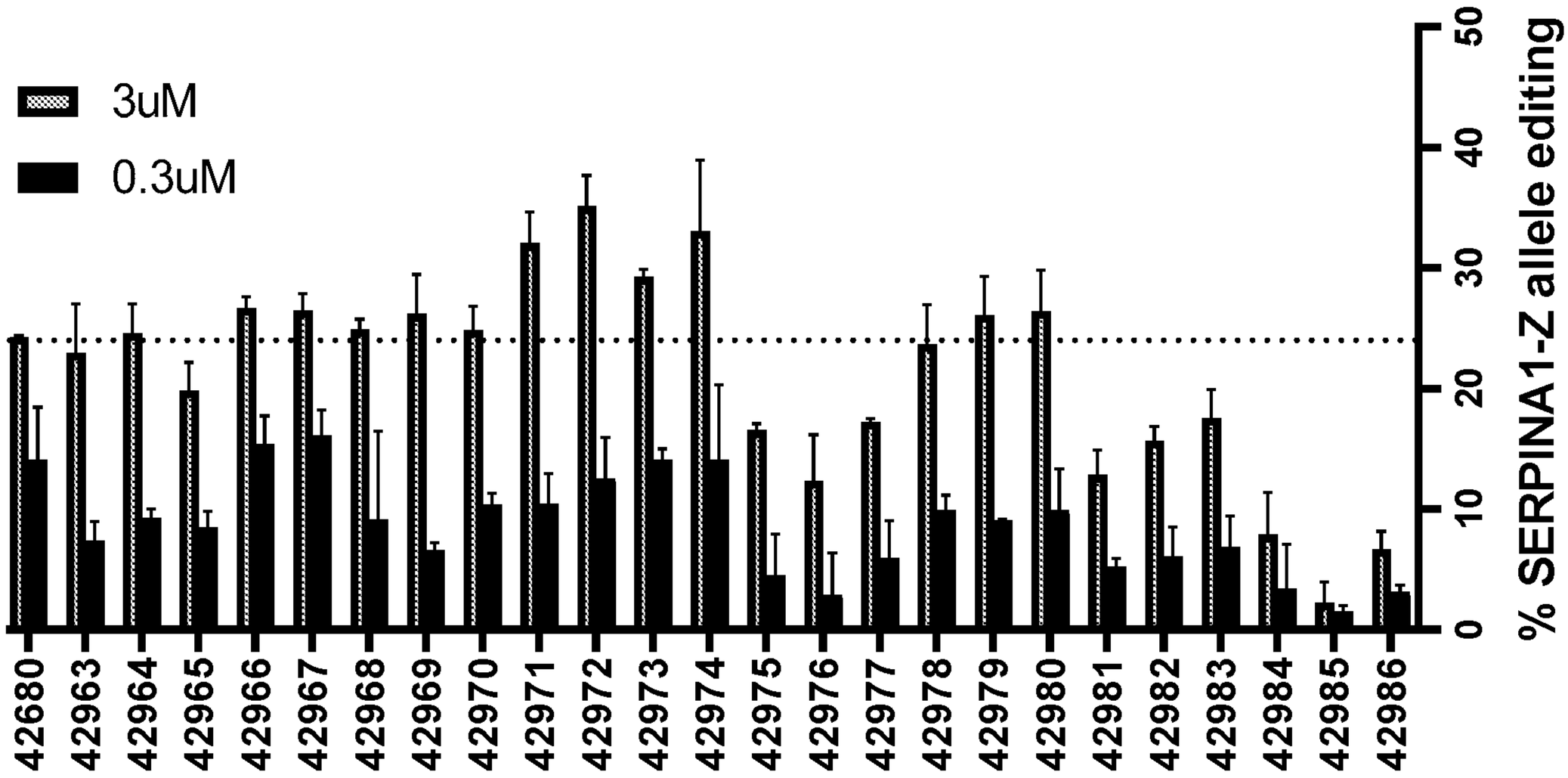


FIG. 10

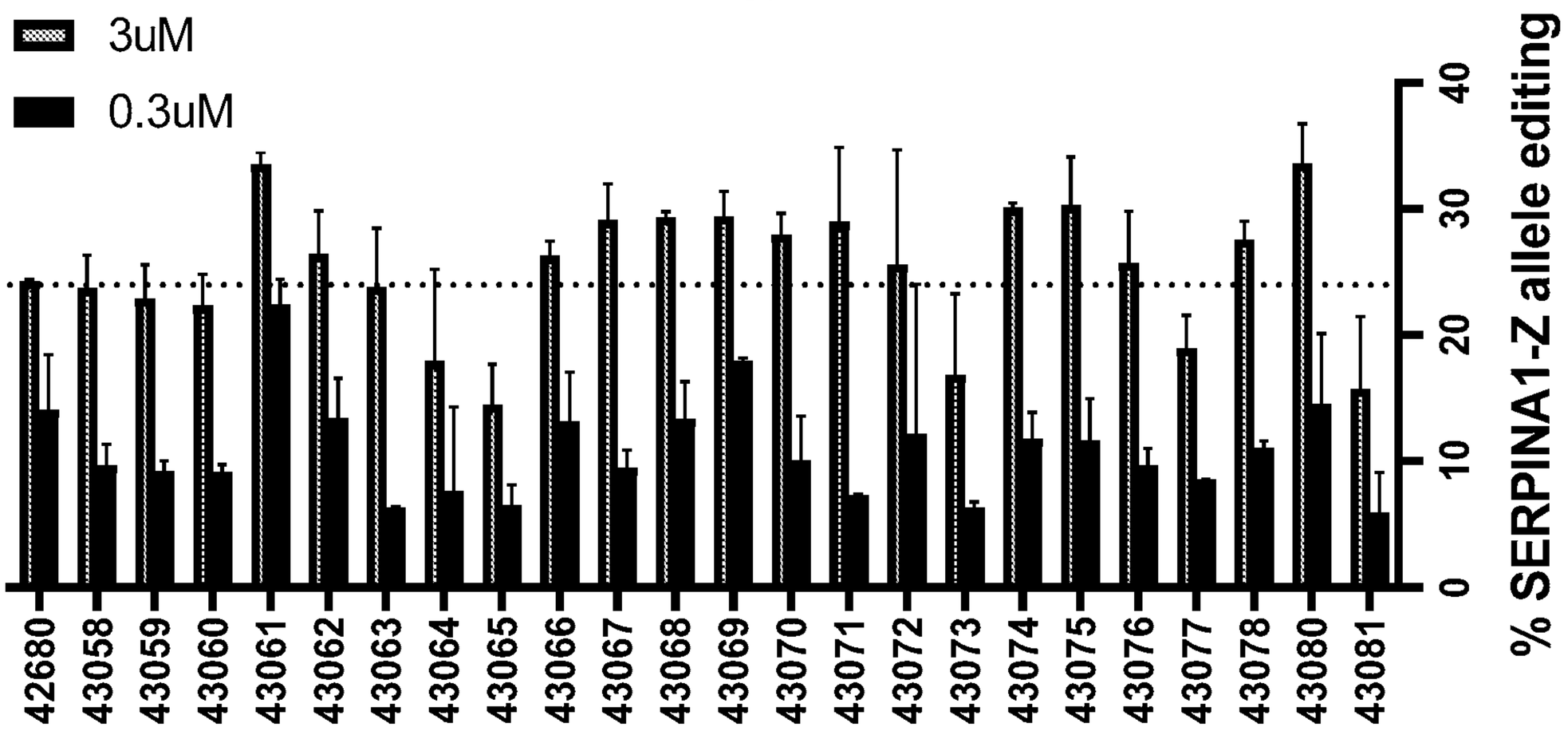


FIG. 11

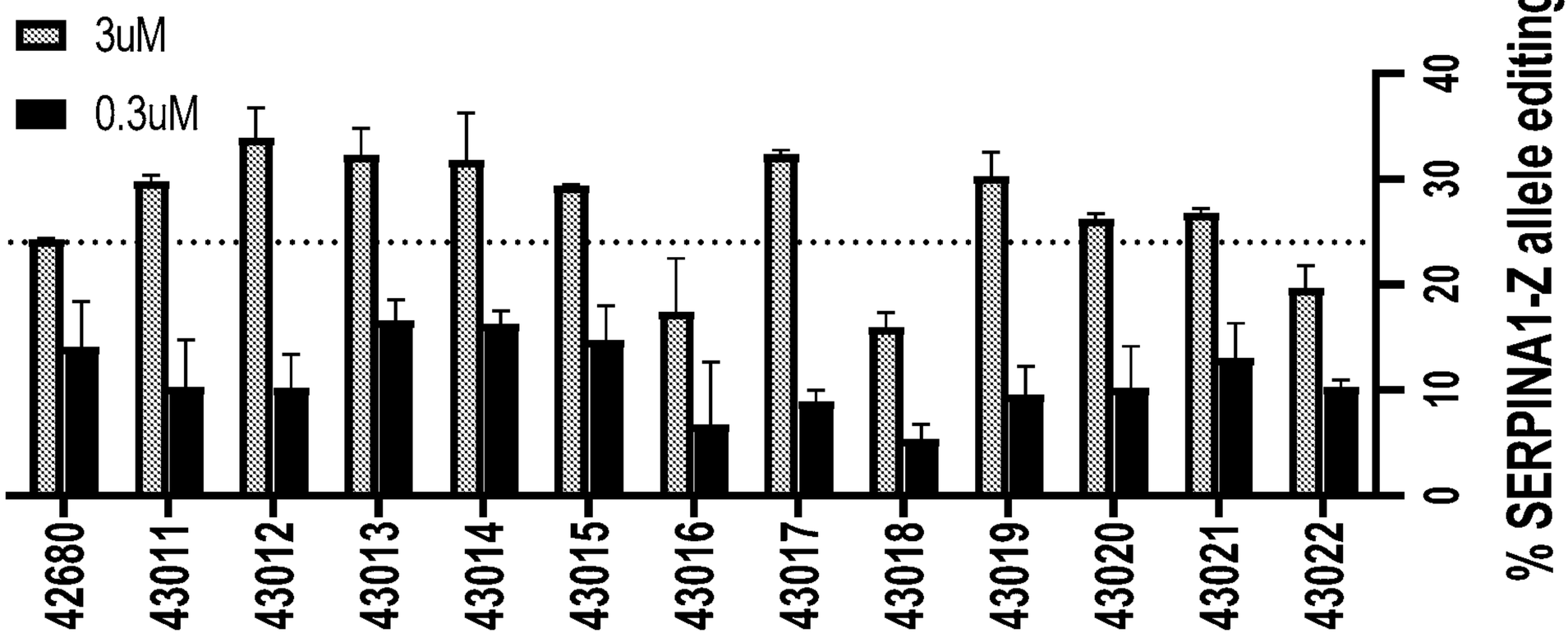


FIG. 12

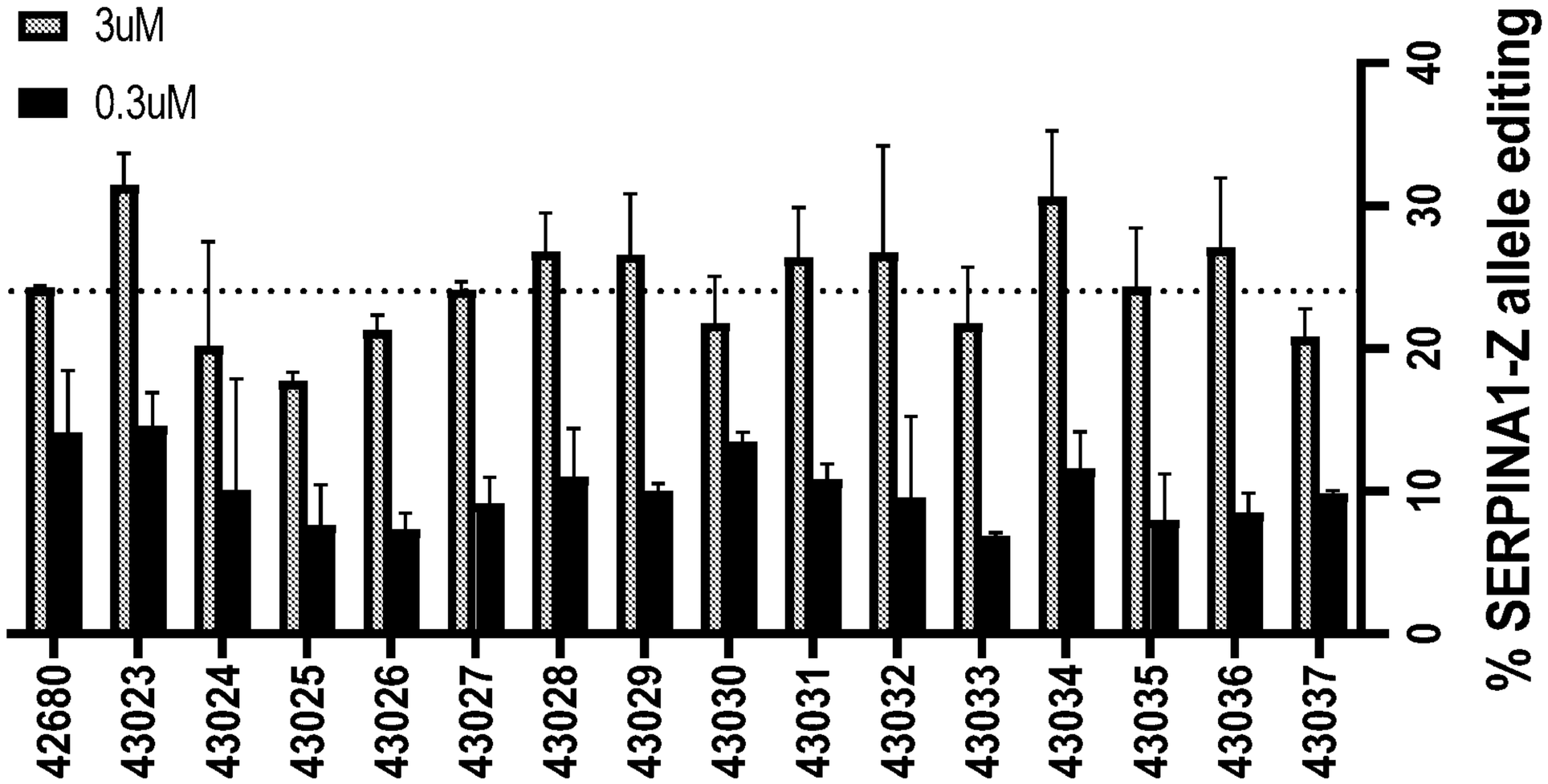


FIG. 13

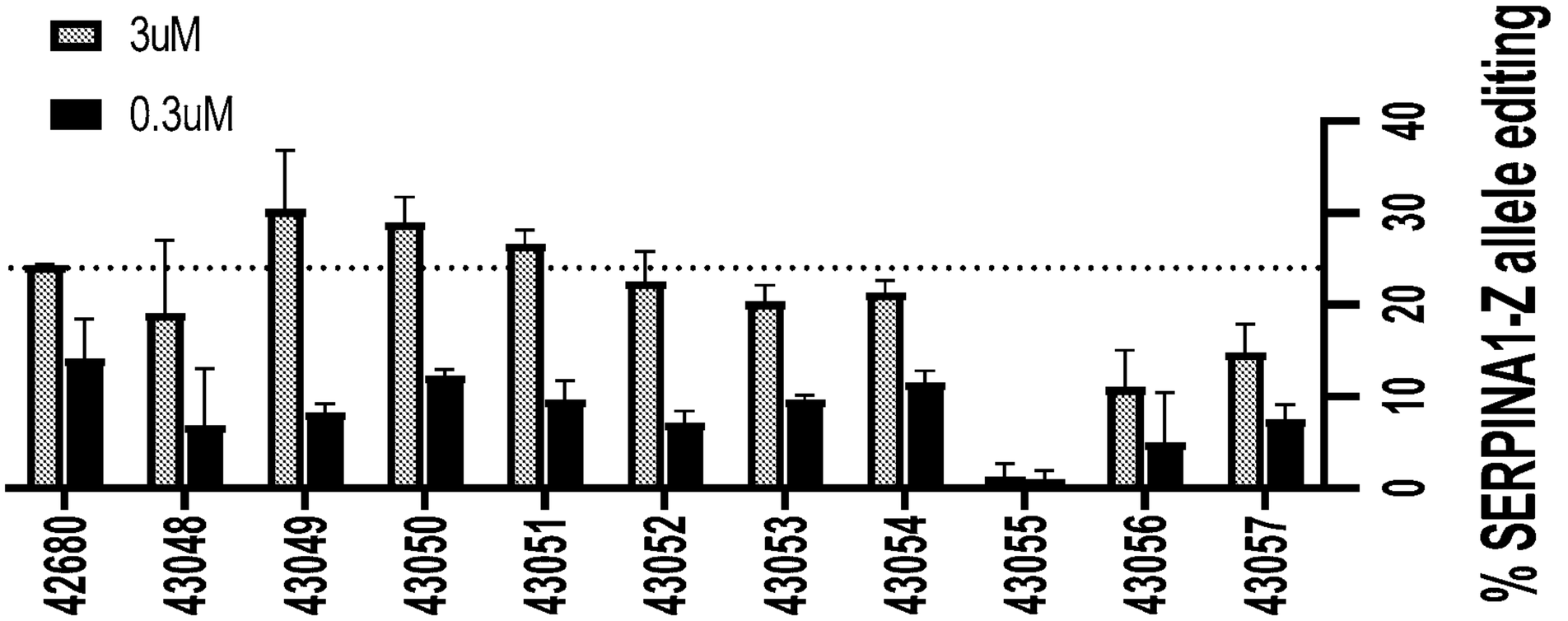


FIG. 14

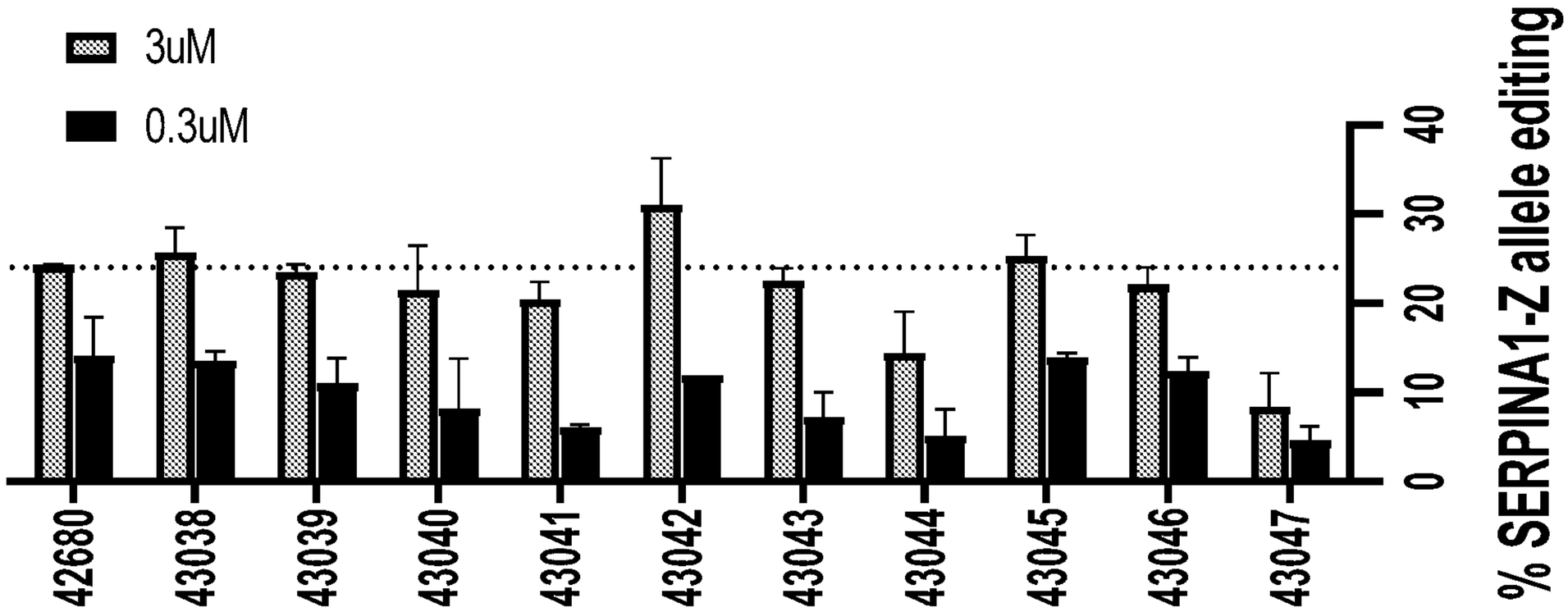


FIG. 15

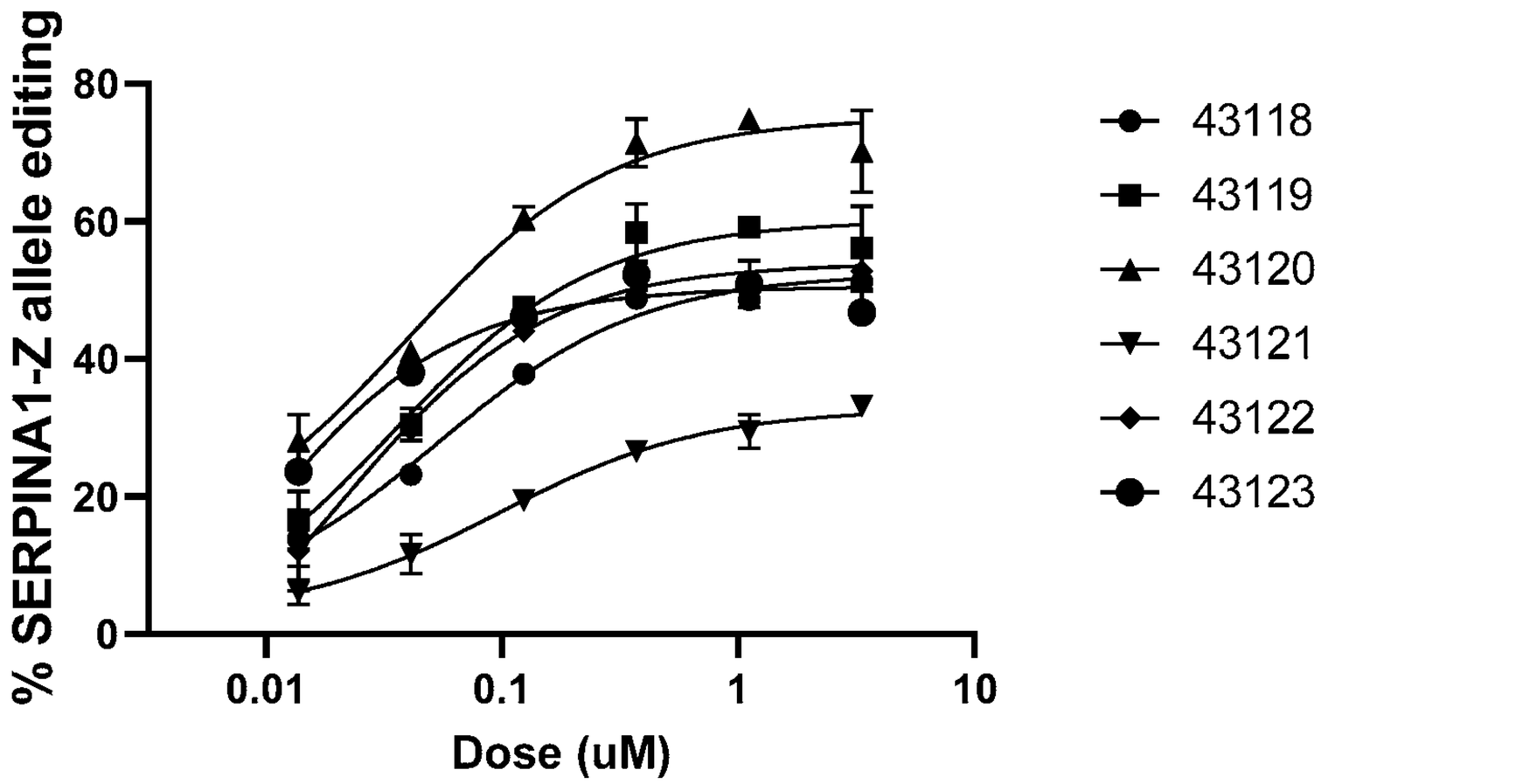

% SERPINA1-Z allele editing
80
60
40
20
0
0.01
0.1
1
10
Dose (uM)
43118
43119
43120
43121
43122
43123

FIG. 16

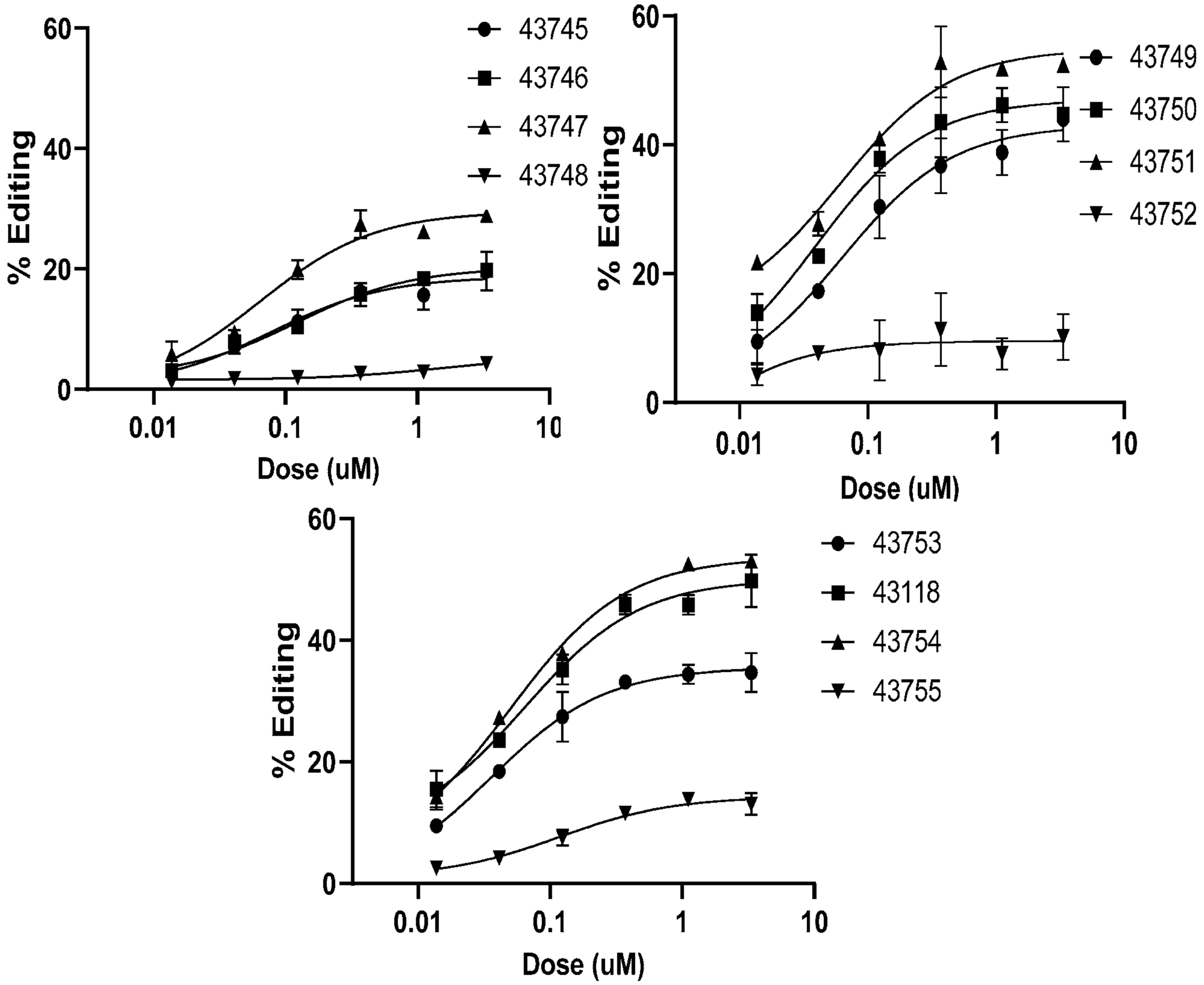
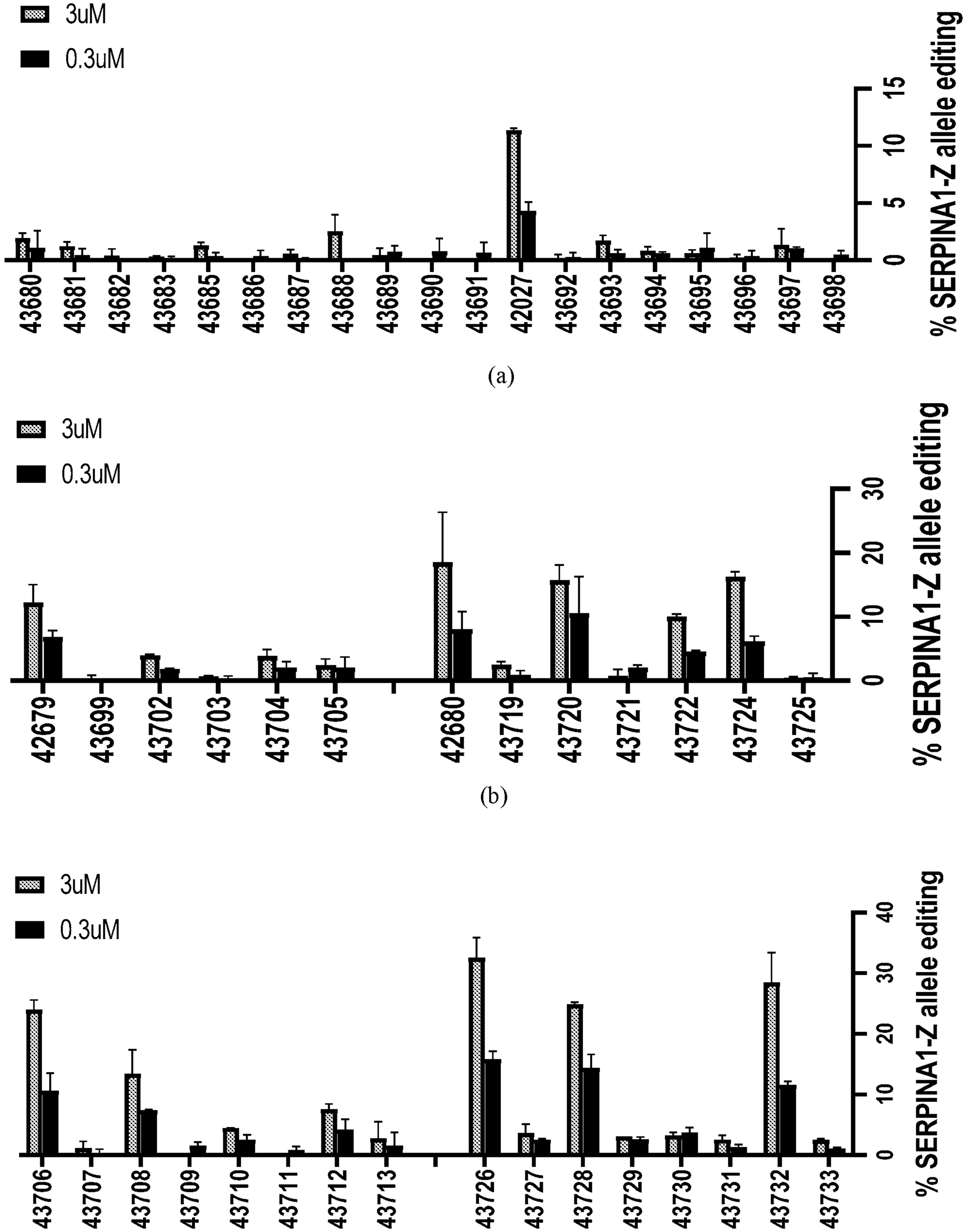

% Editing
60
40
20
0
0.01
0.1
1
10
Dose (uM)
43745
43746
43747
43748
43749
43750
43751
43752
43753
43118
43754
43755

FIG. 17


3uM
0.3uM
% SERPINA1-Z allele editing
0
5
10
15
43680
43681
43682
43683
43685
43686
43687
43688
43689
43690
43691
42027
43692
43693
43694
43695
43696
43697
43698

(a)

3uM
0.3uM
% SERPINA1-Z allele editing
0
10
20
30
42679
43699
43702
43703
43704
43705
42680
43719
43720
43721
43722
43724
43725

(b)

3uM
0.3uM
% SERPINA1-Z allele editing
0
10
20
30
40
43706
43707
43708
43709
43710
43711
43712
43713
43726
43727
43728
43729
43730
43731
43732
43733

(c)

FIG. 18

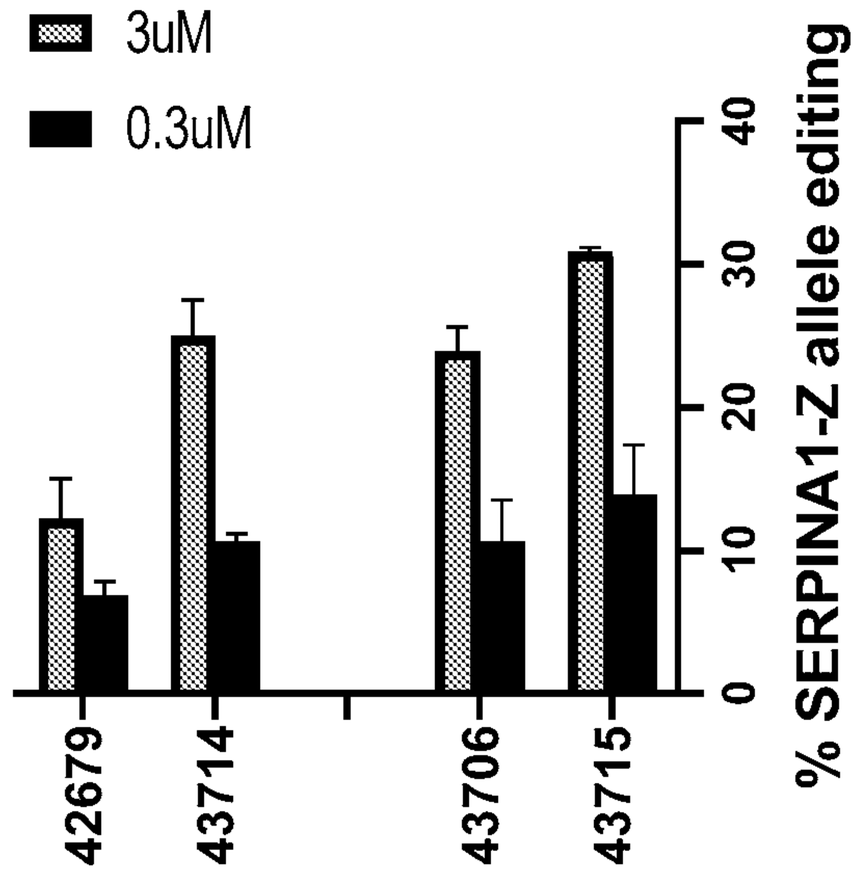


FIG. 19

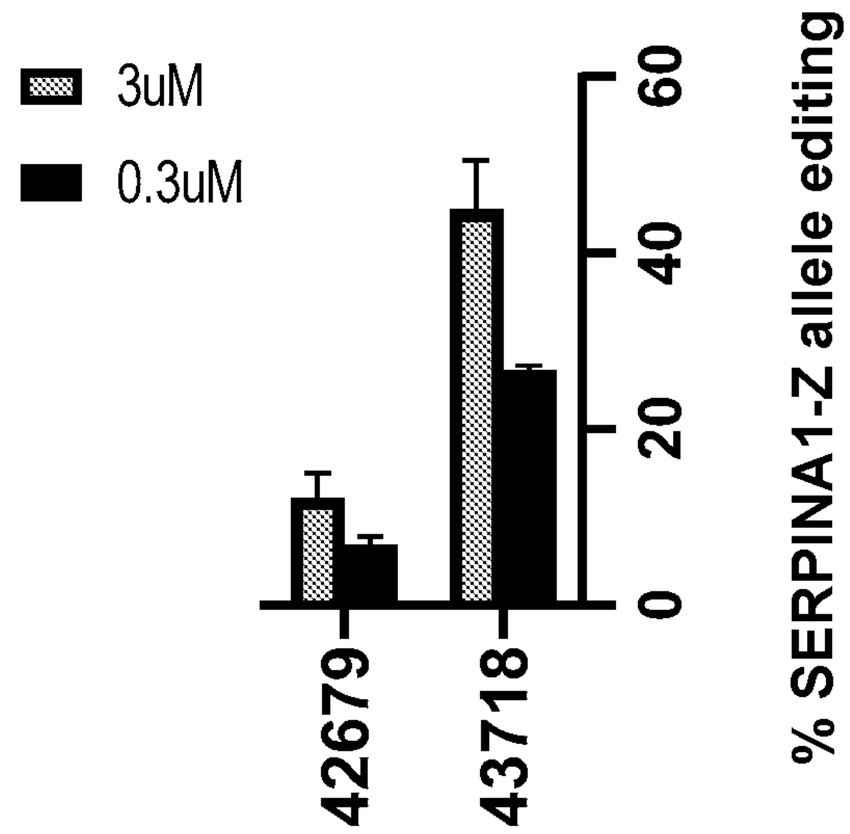


FIG. 20

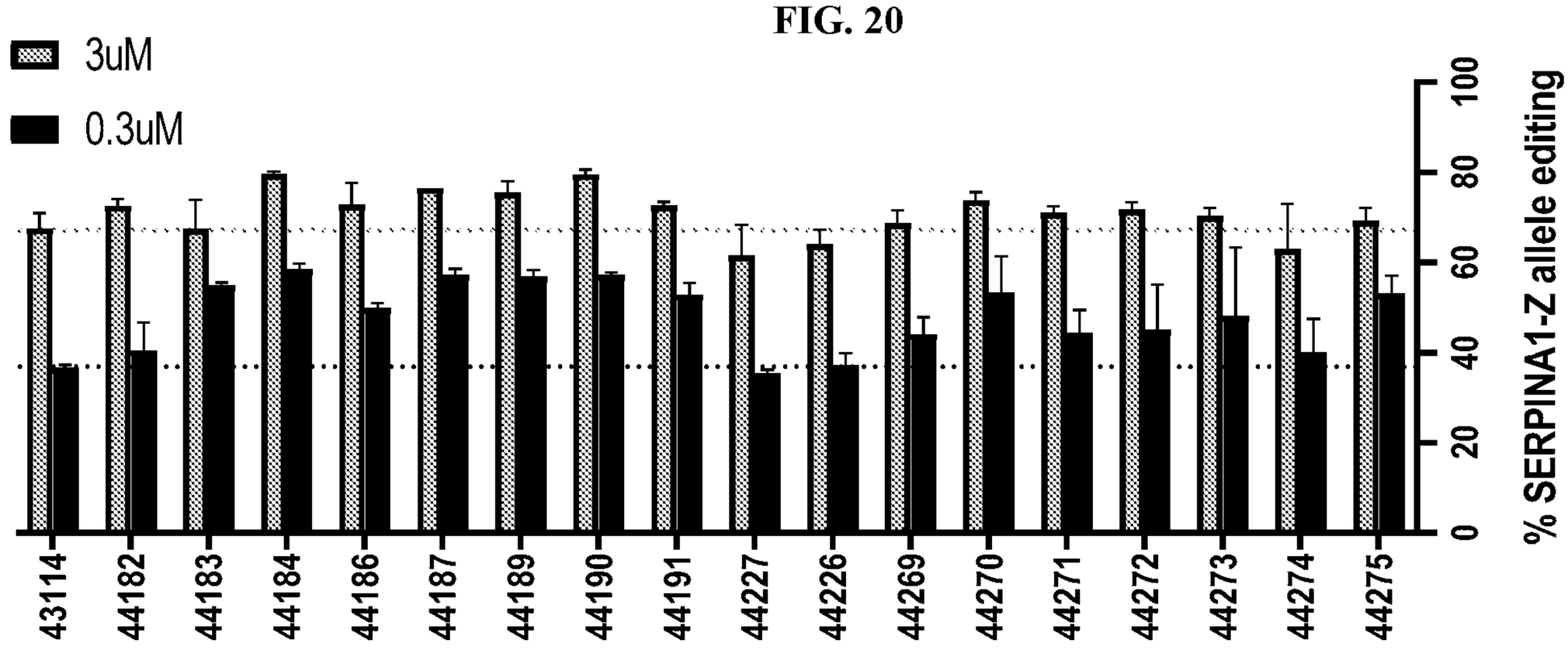


FIG. 21

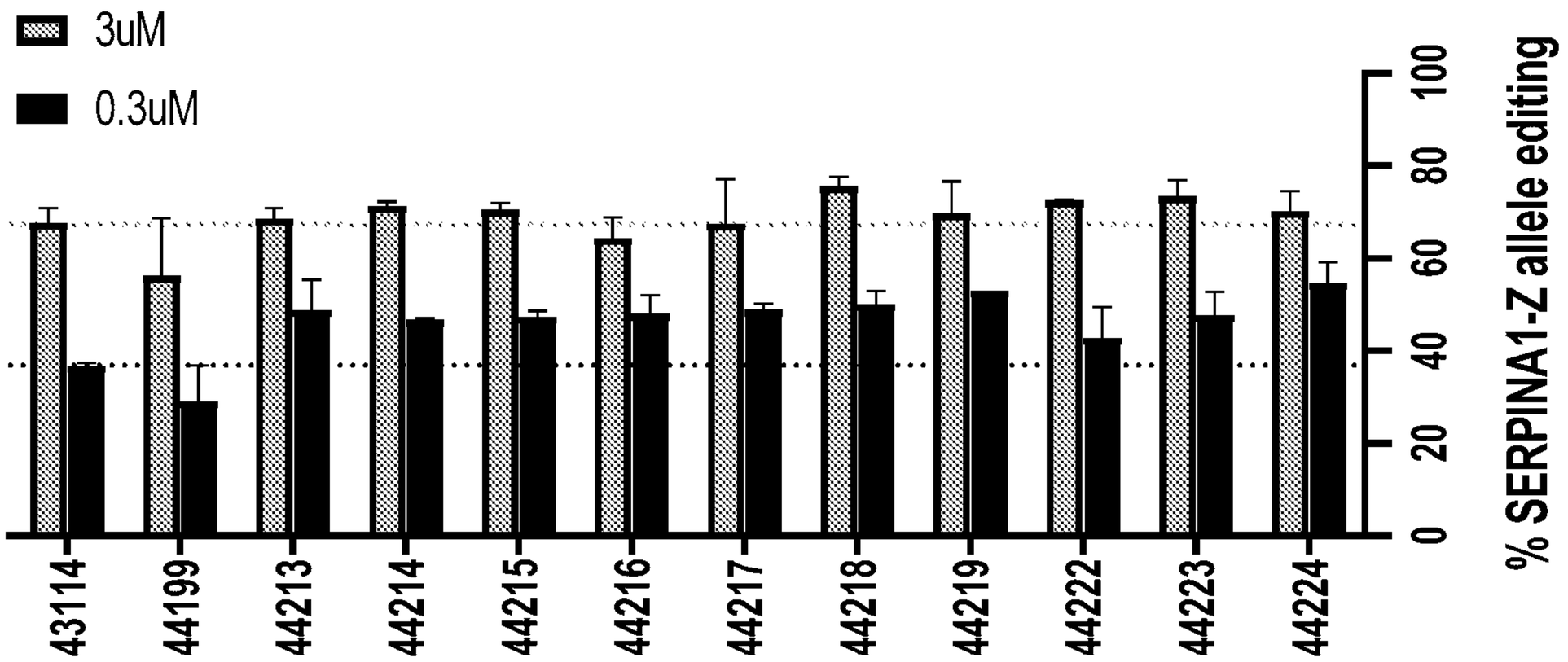


FIG. 22

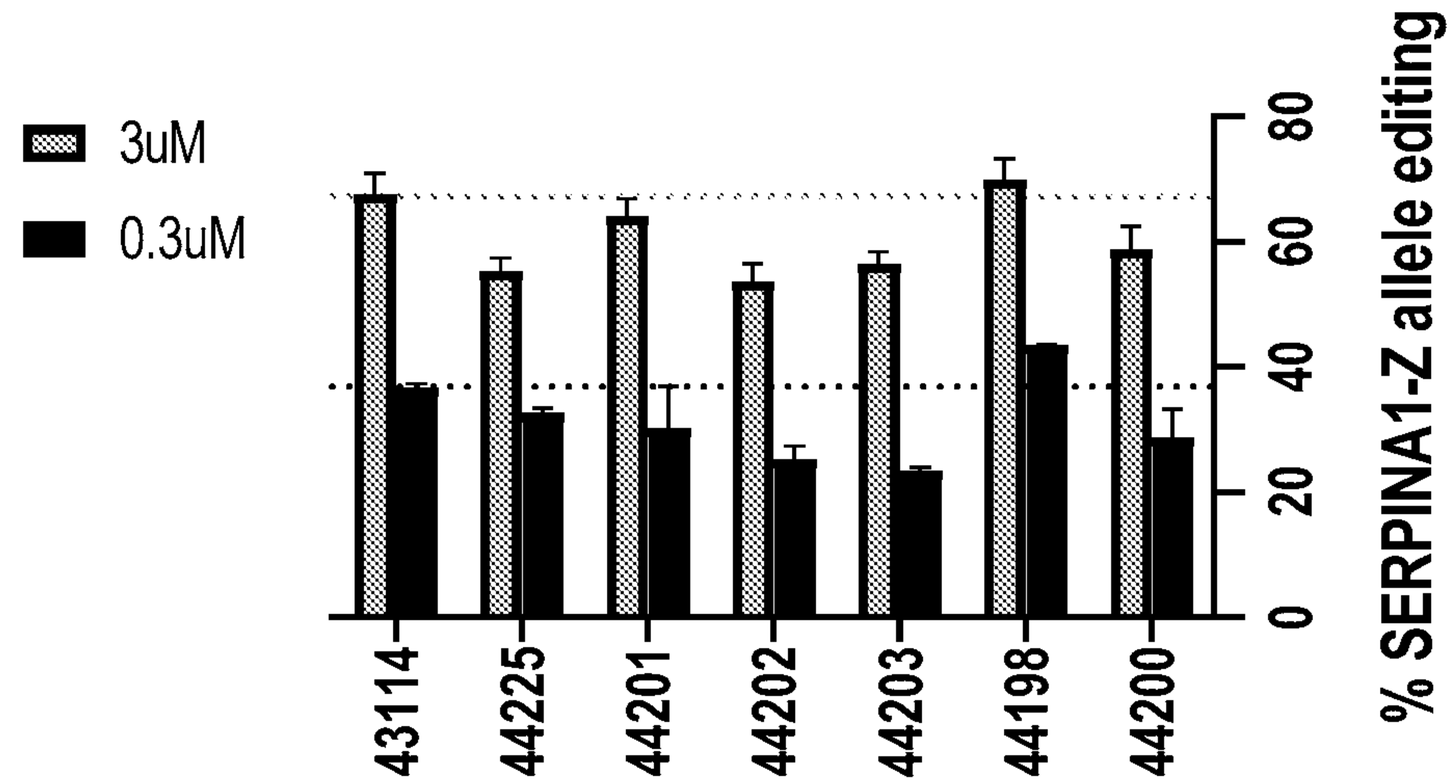


FIG. 23

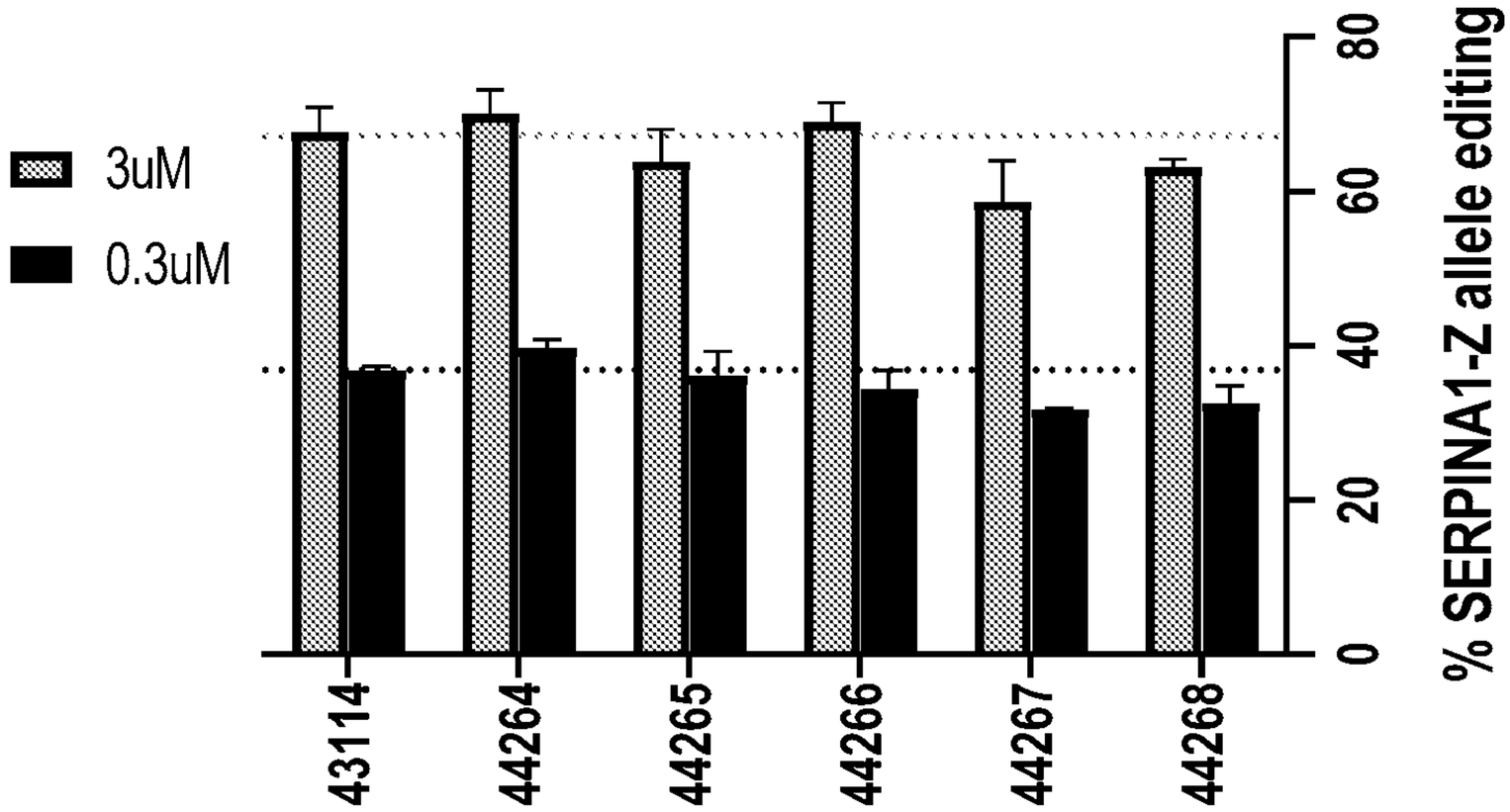


FIG. 24

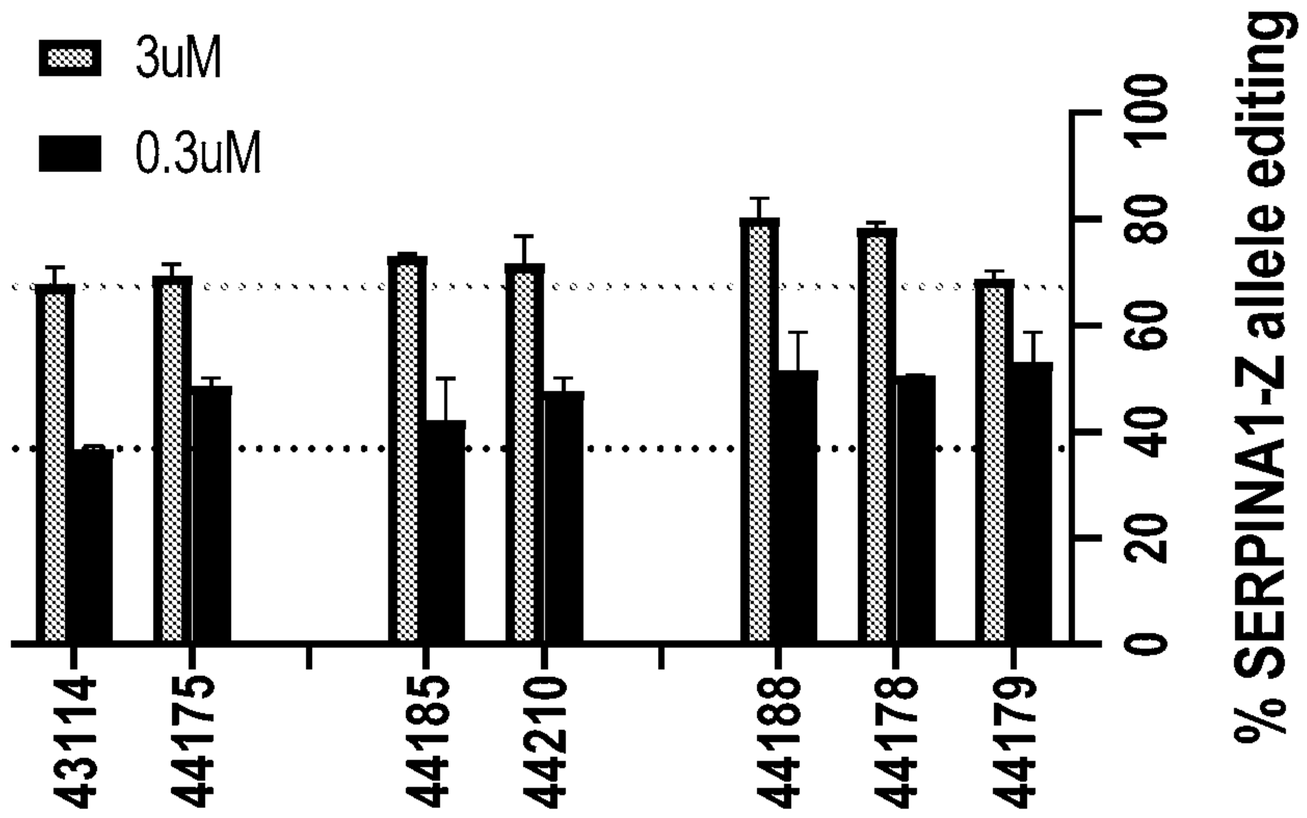


FIG. 25

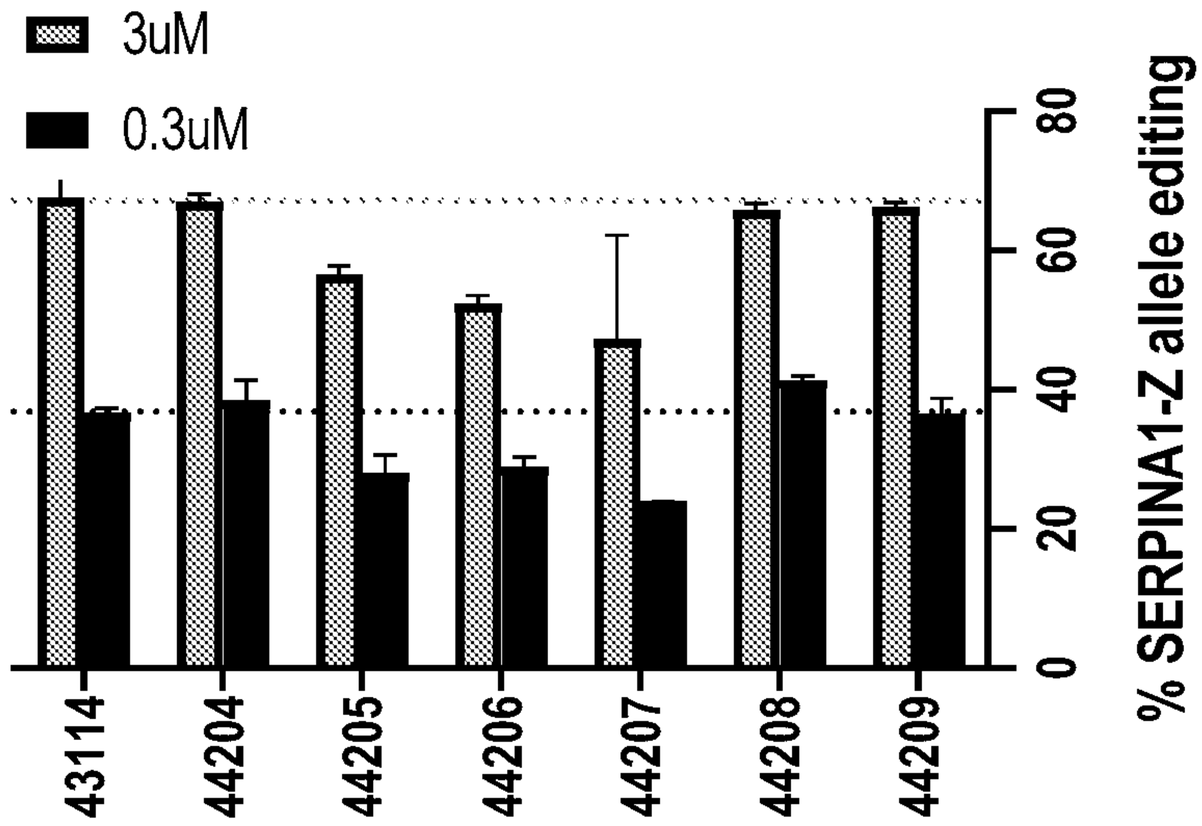


FIG. 26

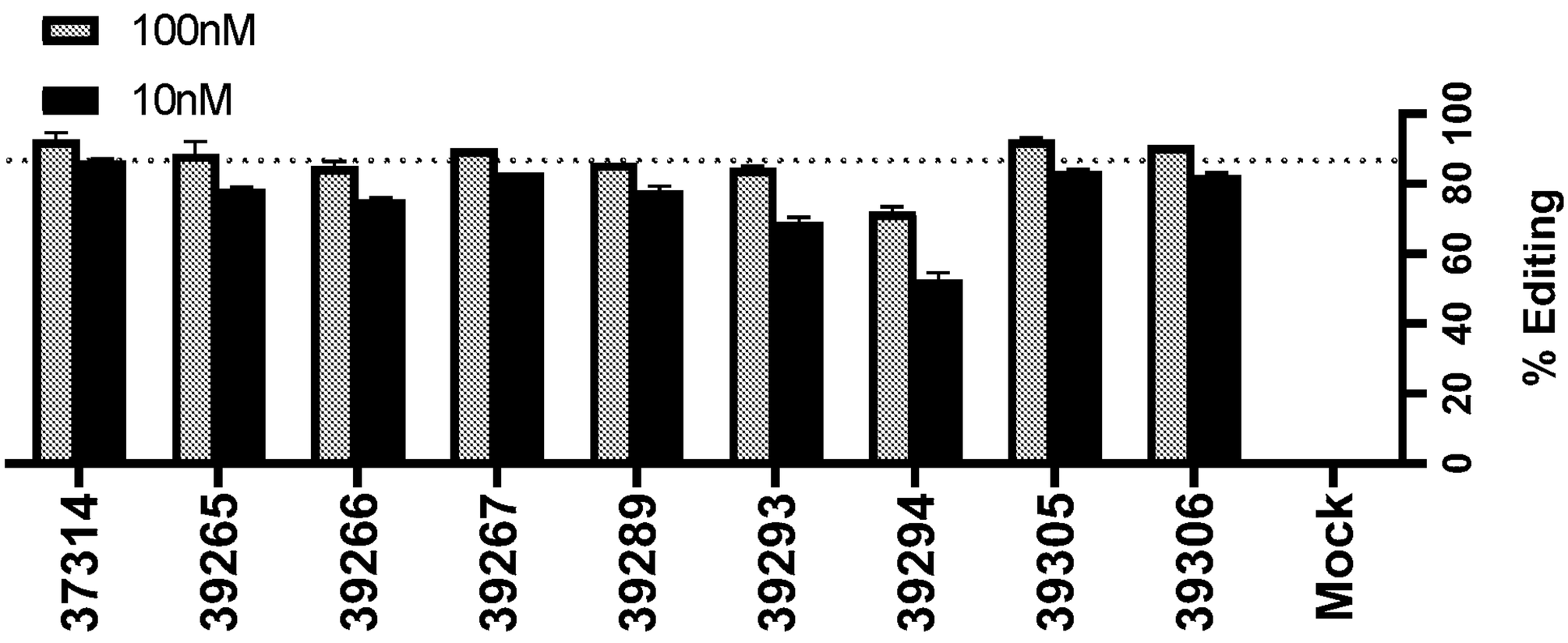


FIG. 27

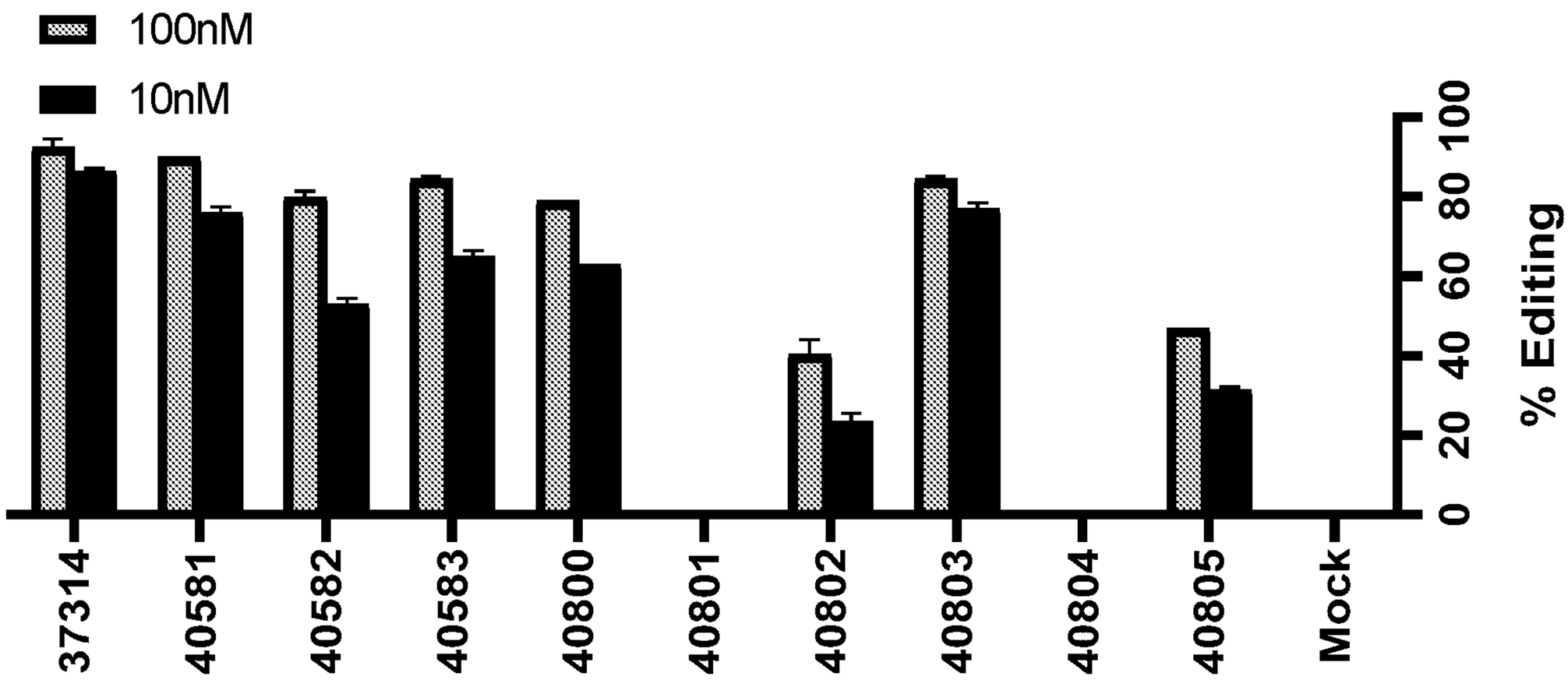


FIG. 28

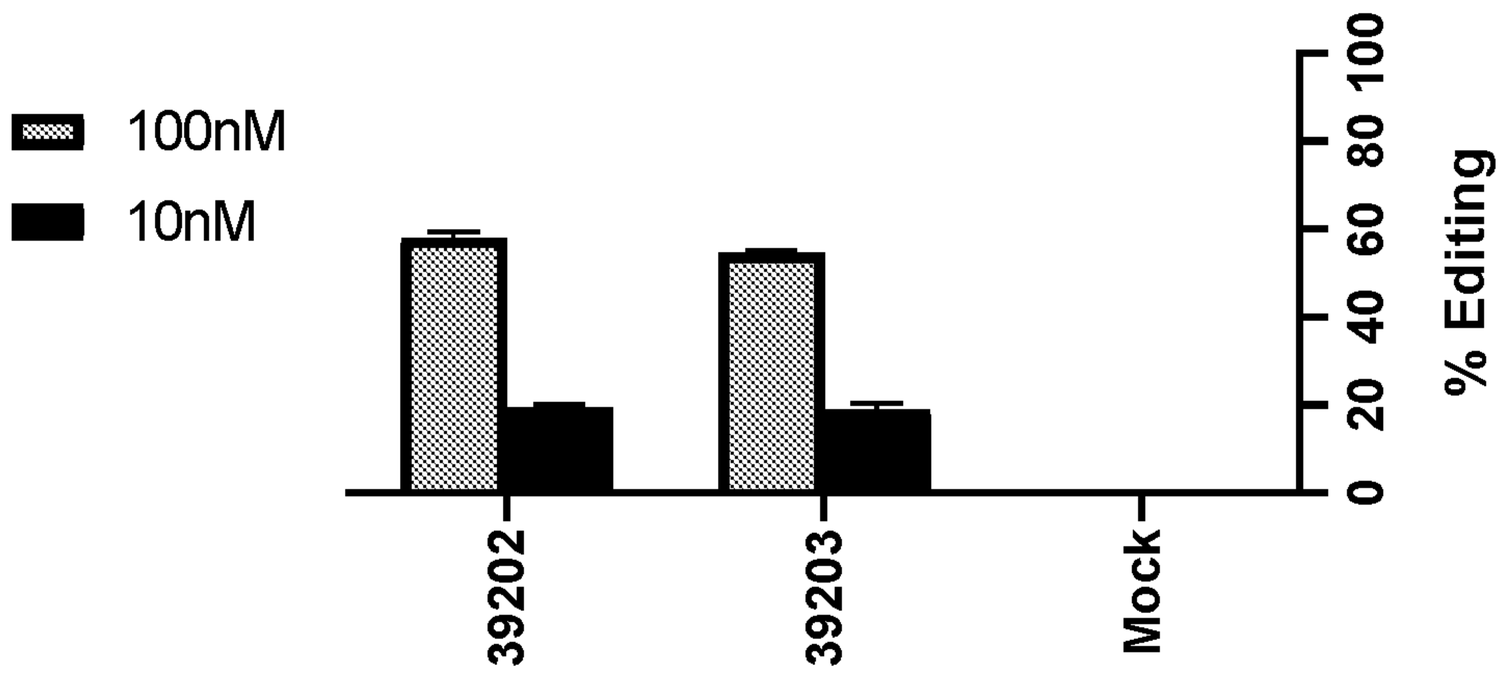


FIG. 29

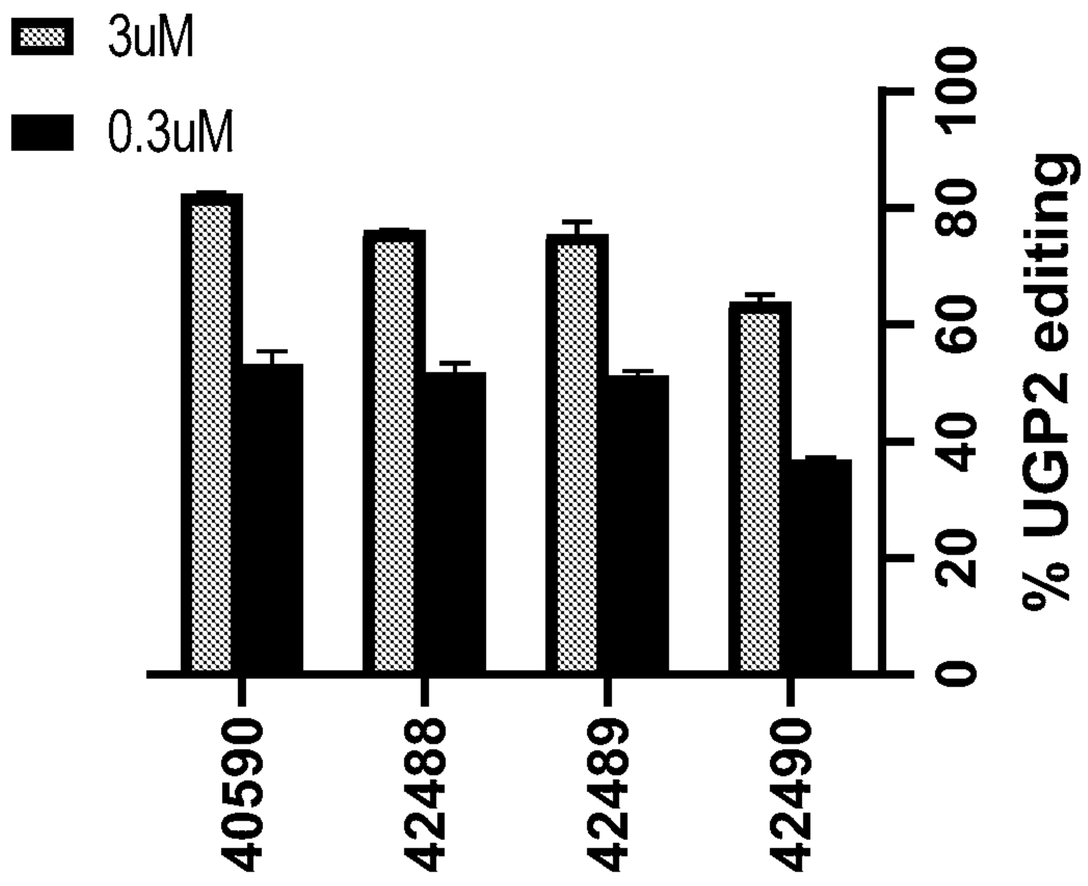
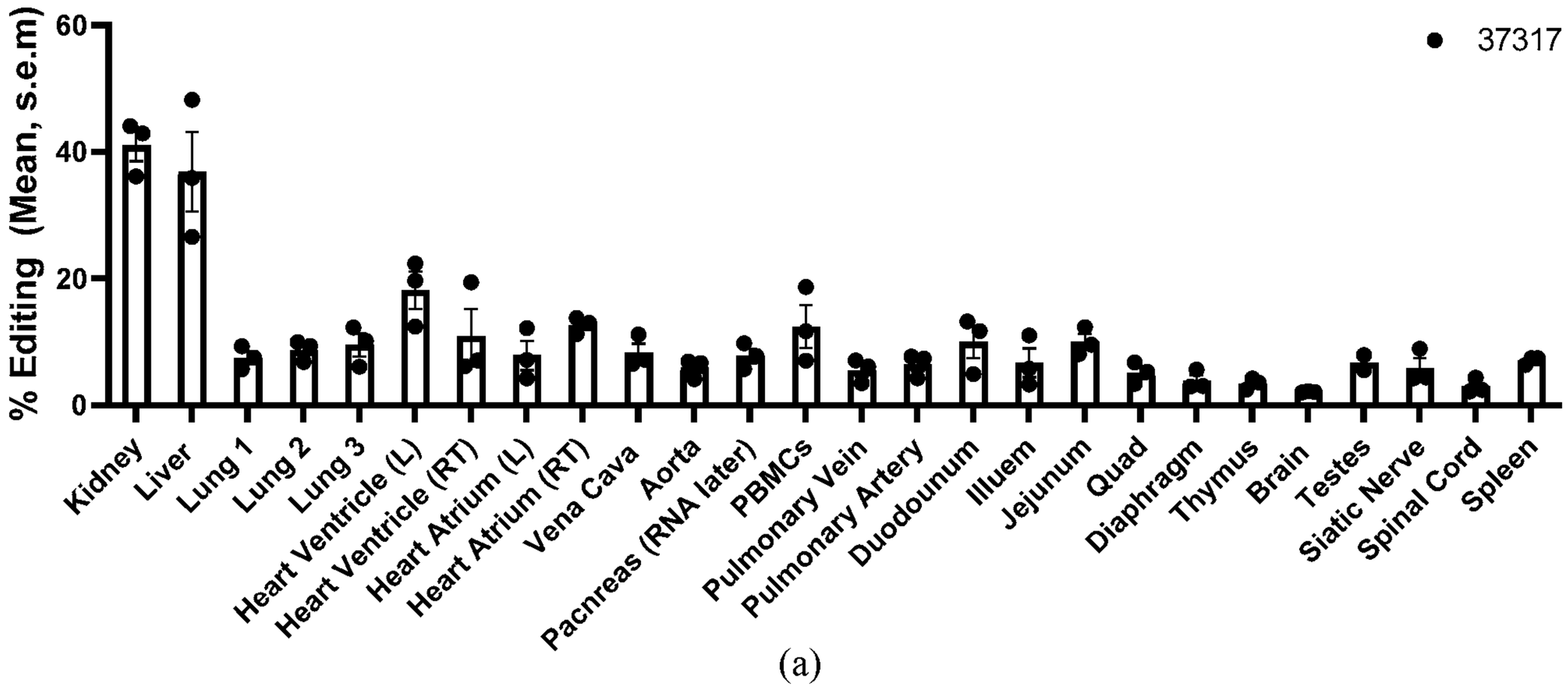
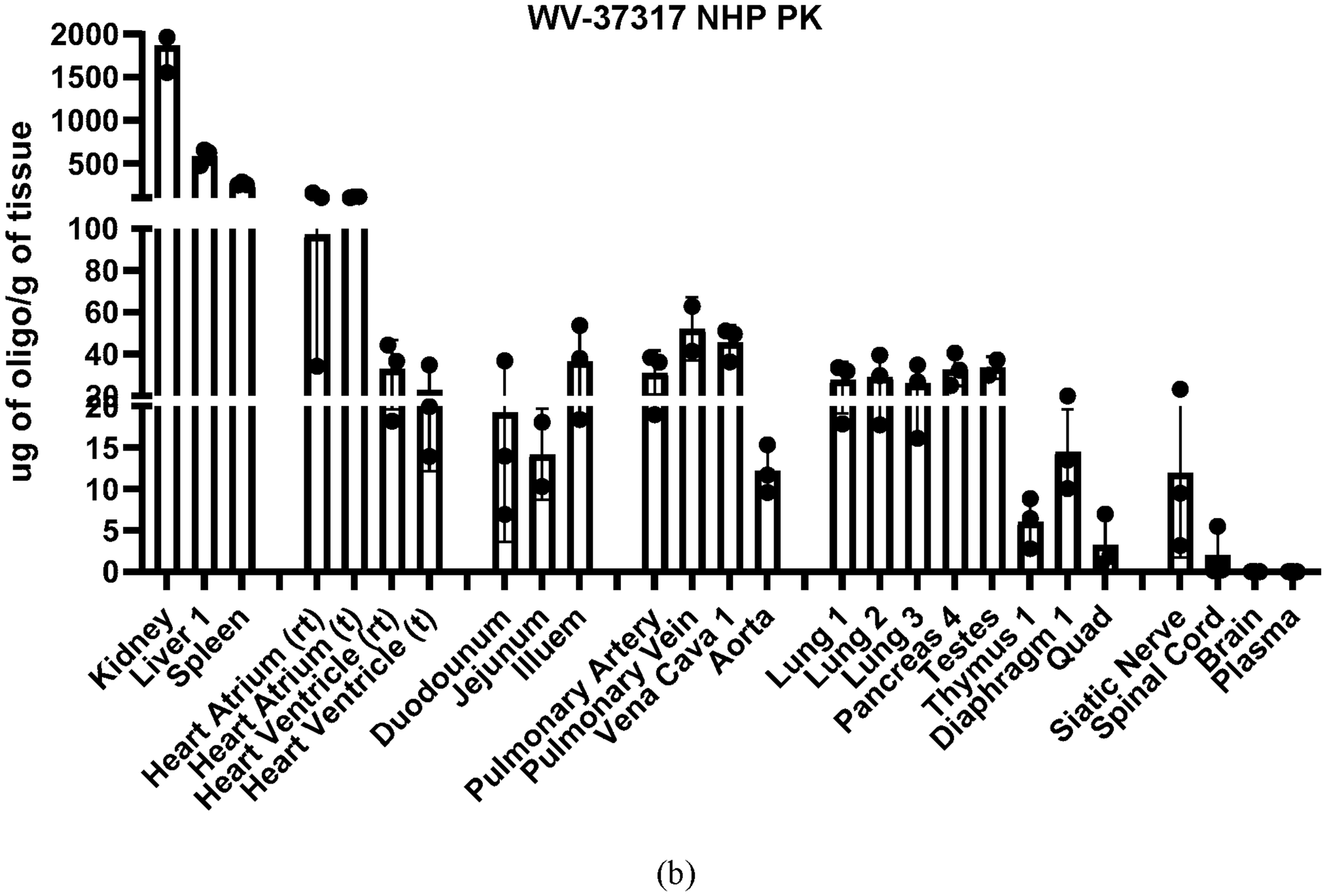


FIG. 30

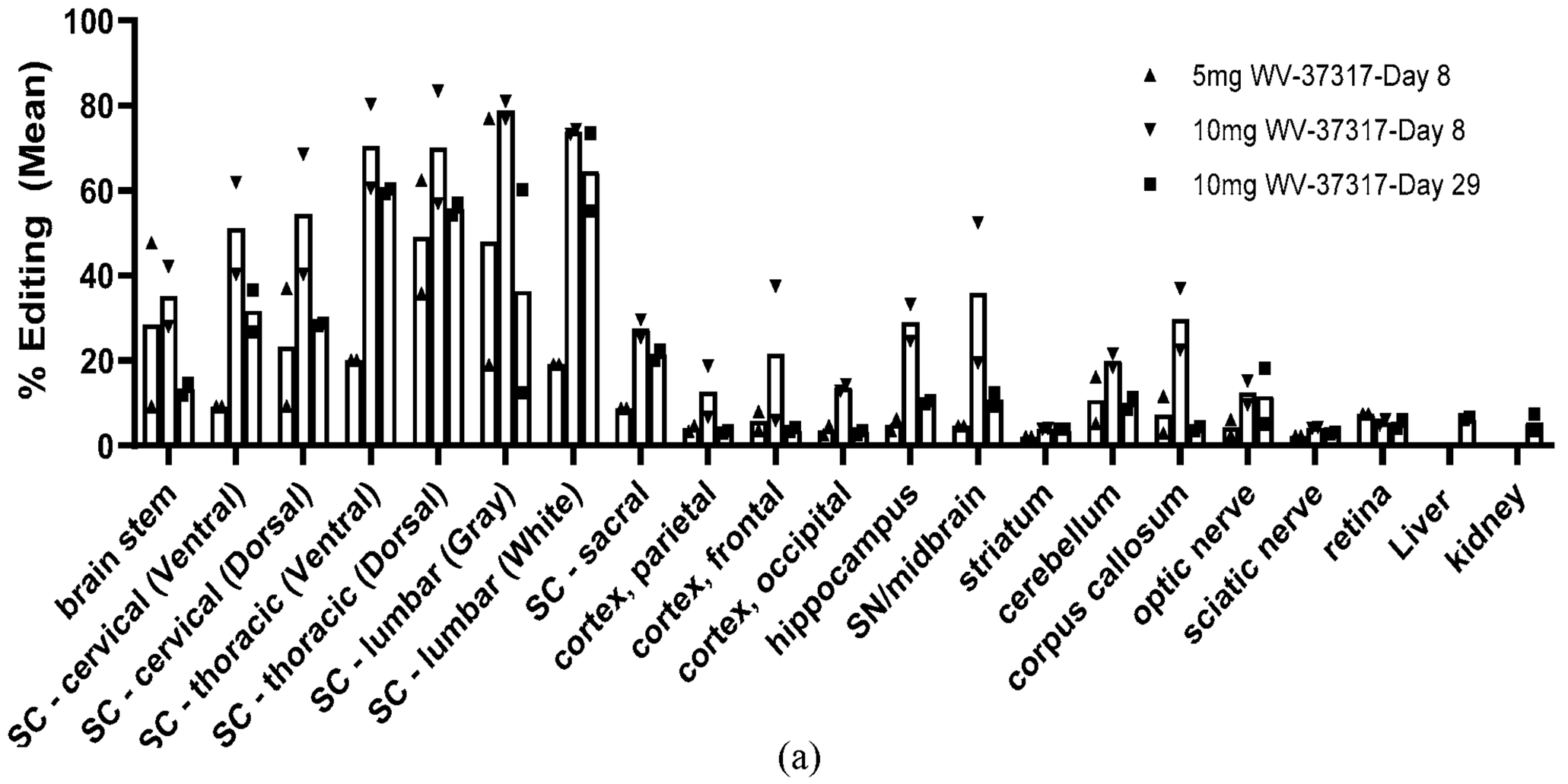

in vivo ACTB editing in NHP
Systemic administration - 50mpk, 7 days
37317
% Editing (Mean, s.e.m)
60
40
20
0
Kidney
Liver
Lung 1
Lung 2
Lung 3
Heart Ventricle (L)
Heart Ventricle (RT)
Heart Atrium (L)
Heart Atrium (RT)
Vena Cava
Aorta
Pacnreas (RNA later)
PBMCs
Pulmonary Vein
Pulmonary Artery
Duodounum
Illuem
Jejunum
Quad
Diaphragm
Thymus
Brain
Testes
Siatic Nerve
Spinal Cord
Spleen

(a)

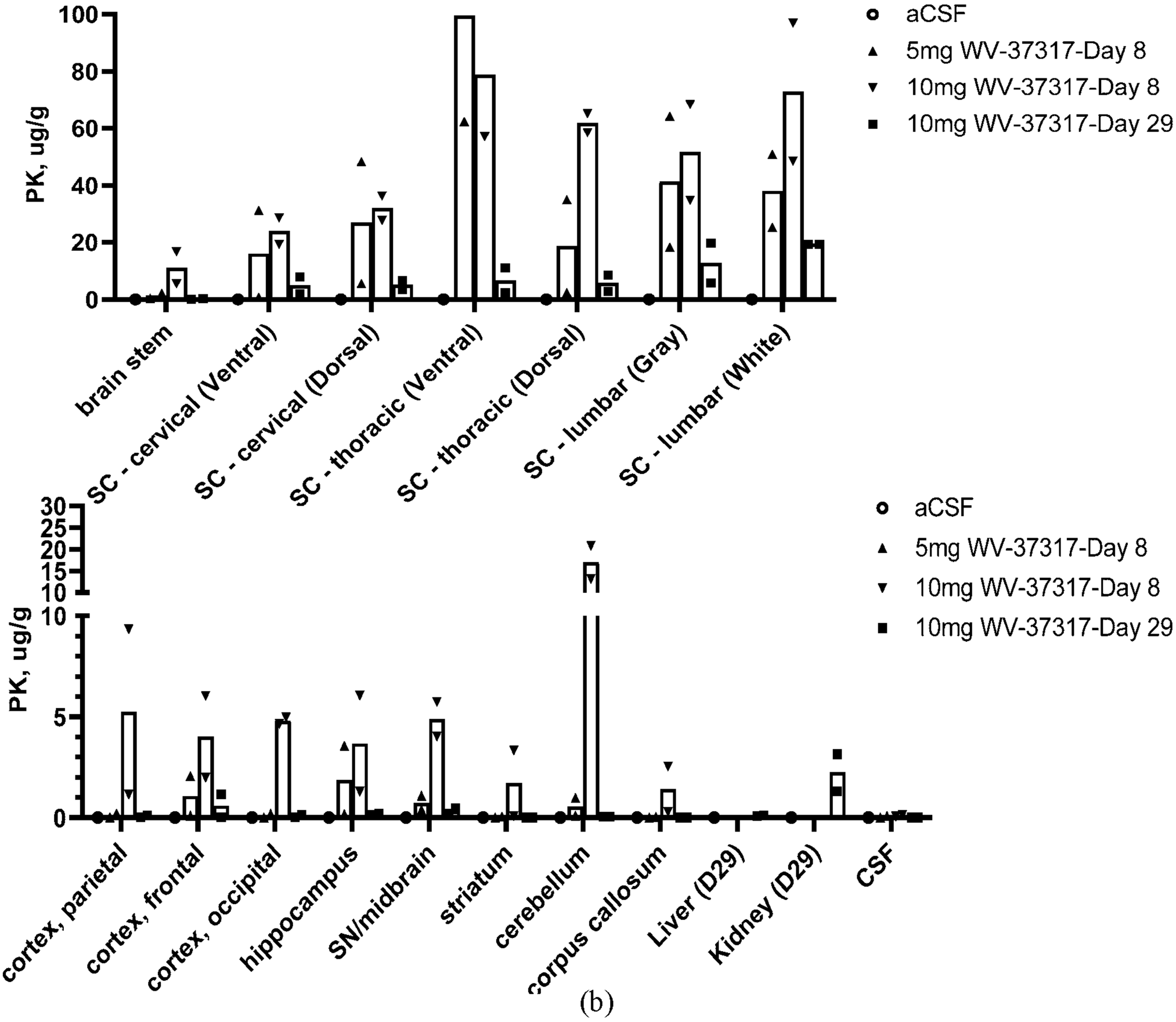

WV-37317 NHP PK
ug of oligo/g of tissue
2000
1500
1000
500
100
80
60
40
20
15
10
5
0
Kidney
Liver 1
Spleen
Heart Atrium (rt)
Heart Atrium (t)
Heart Ventricle (rt)
Heart Ventricle (t)
Duodounum
Jejunum
Illuem
Pulmonary Artery
Pulmonary Vein
Vena Cava 1
Aorta
Lung 1
Lung 2
Lung 3
Pancreas 4
Testes
Thymus 1
Diaphragm 1
Quad
Siatic Nerve
Spinal Cord
Brain
Plasma

(b)

FIG. 31


in vivo ACTB editing in NHP
Intrathecal administration
% Editing (Mean)
100
80
60
40
20
0
5mg WV-37317-Day 8
10mg WV-37317-Day 8
10mg WV-37317-Day 29
brain stem
SC - cervical (Ventral)
SC - cervical (Dorsal)
SC - thoracic (Ventral)
SC - thoracic (Dorsal)
SC - lumbar (Gray)
SC - lumbar (White)
SC - sacral
cortex, parietal
cortex, frontal
cortex, occipital
hippocampus
SN/midbrain
striatum
cerebellum
corpus callosum
optic nerve
sciatic nerve
retina
Liver
kidney

(a)


PK, ug/g
100
80
60
40
20
0
aCSF
5mg WV-37317-Day 8
10mg WV-37317-Day 8
10mg WV-37317-Day 29
brain stem
SC - cervical (Ventral)
SC - cervical (Dorsal)
SC - thoracic (Ventral)
SC - thoracic (Dorsal)
SC - lumbar (Gray)
SC - lumbar (White)
PK, ug/g
30
25
20
15
10
10
5
0
aCSF
5mg WV-37317-Day 8
10mg WV-37317-Day 8
10mg WV-37317-Day 29
cortex, parietal
cortex, frontal
cortex, occipital
hippocampus
SN/midbrain
striatum
cerebellum
corpus callosum
Liver (D29)
Kidney (D29)
CSF

(b)

FIG. 32

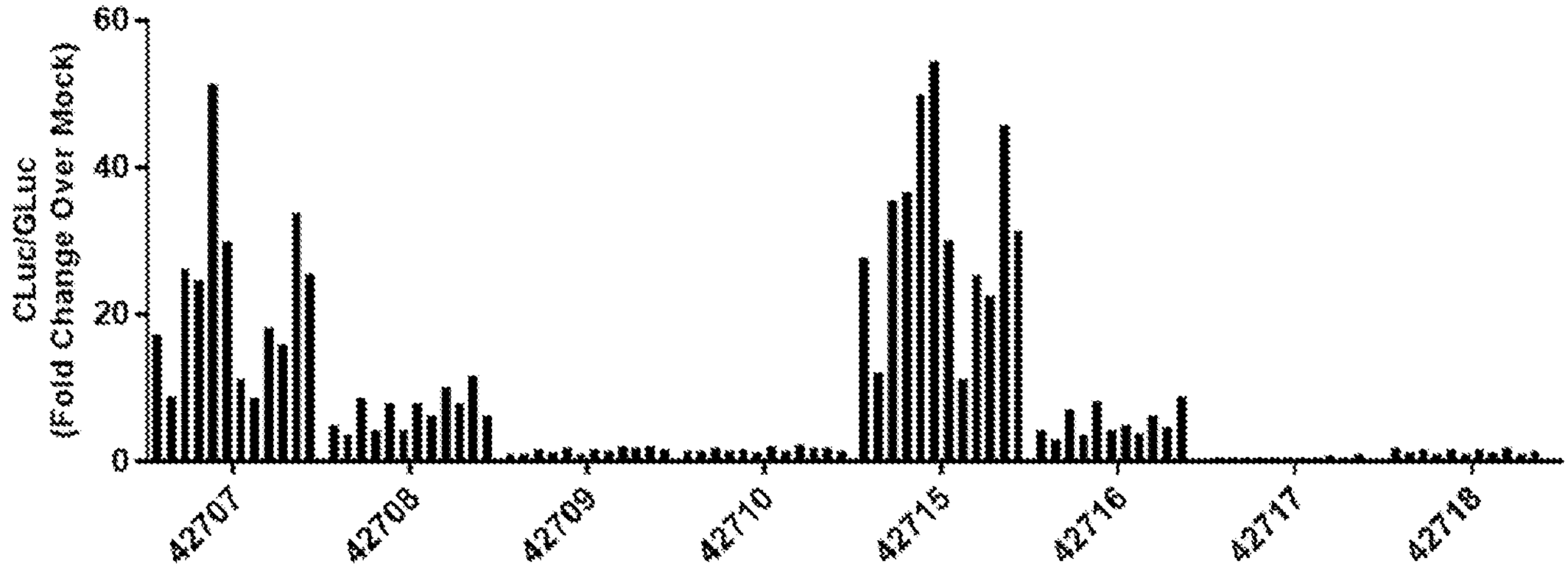

P150
CLuc/GLuc
(Fold Change Over Mock)
60
40
20
0
42707
42708
42709
42710
42715
42716
42717
42718

FIG. 33

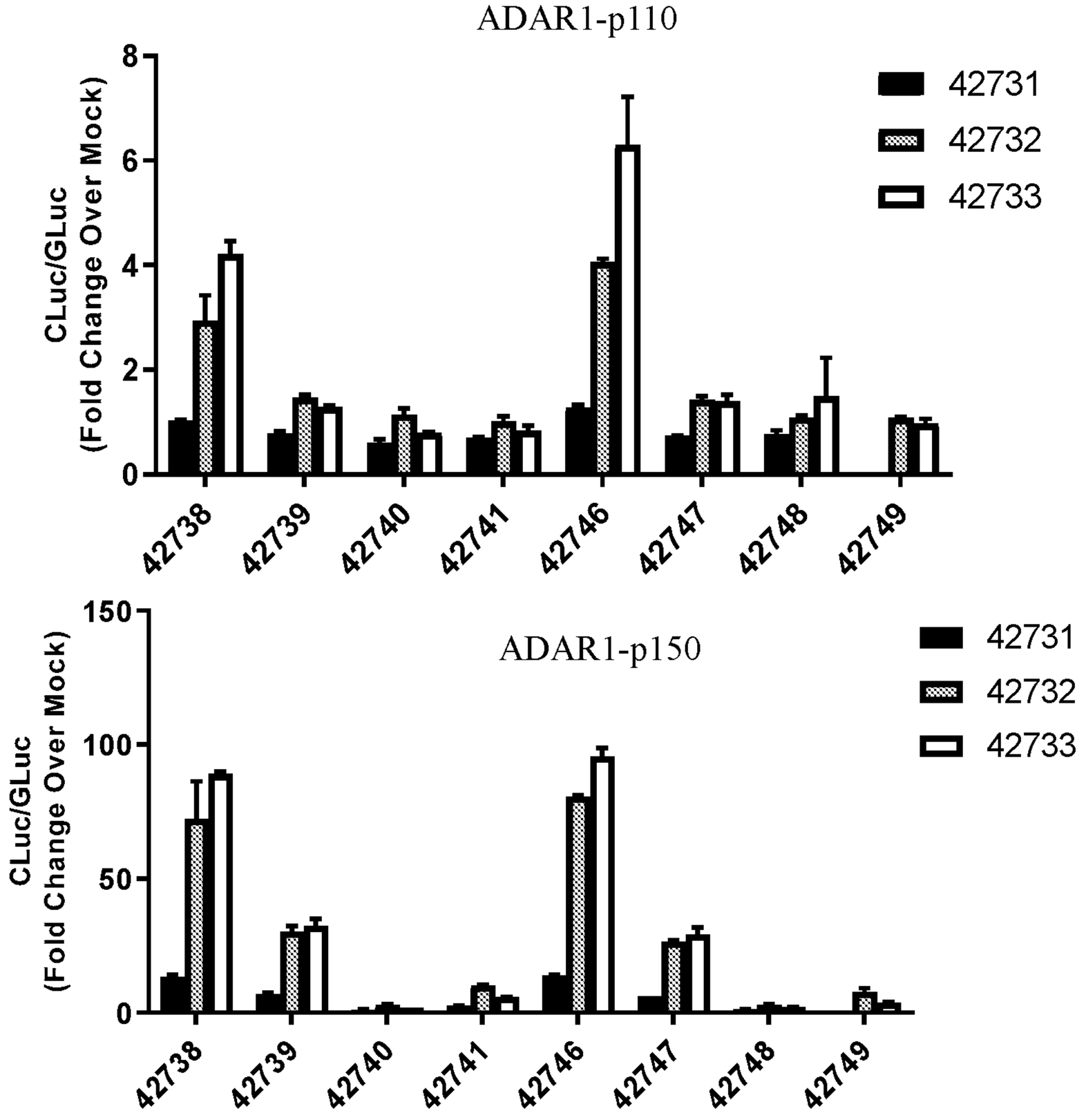
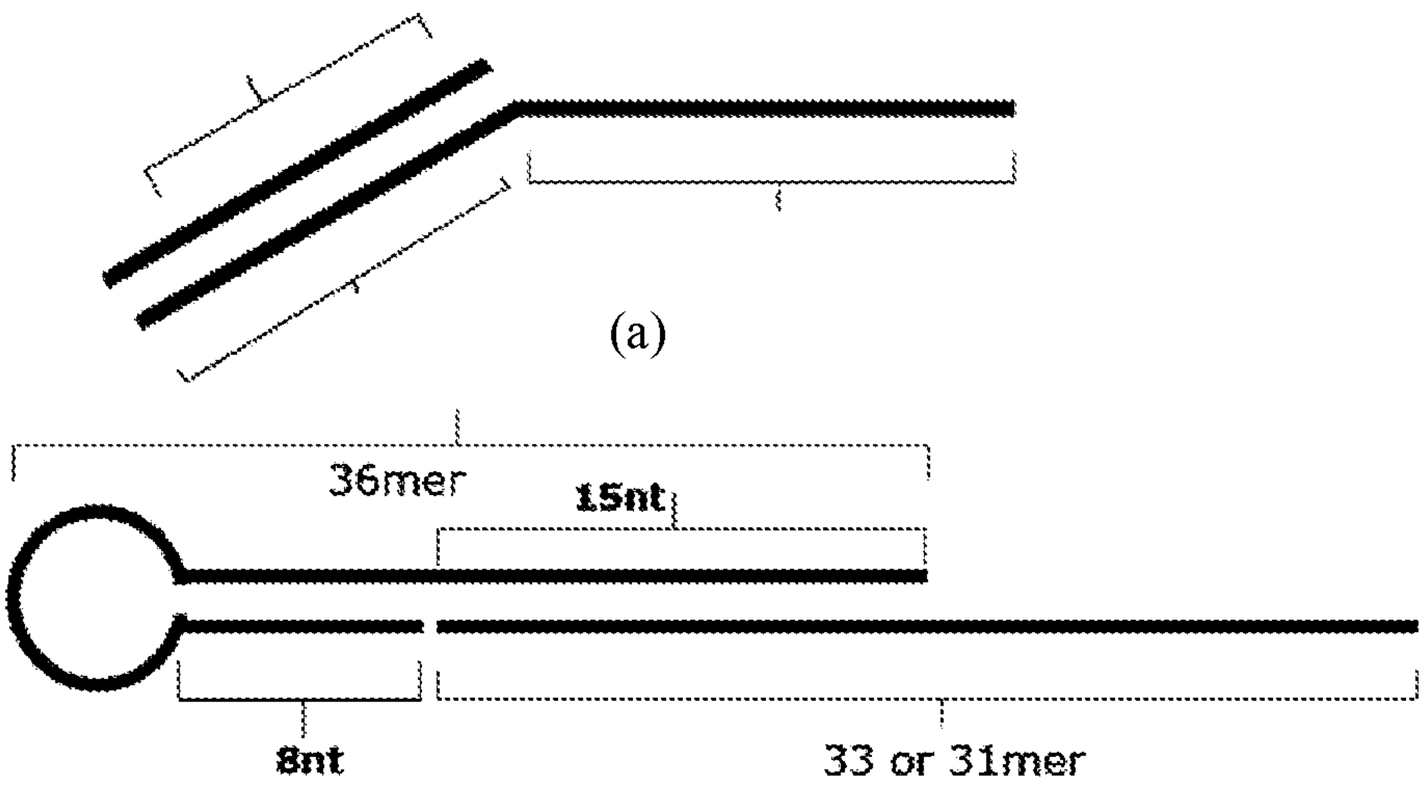

ADAR1-p110
CLuc/GLuc
(Fold Change Over Mock)
8
6
4
2
0
42738
42739
42740
42741
42746
42747
42748
42749
42731
42732
42733
ADAR1-p150
CLuc/GLuc
(Fold Change Over Mock)
150
100
50
0
42738
42739
42740
42741
42746
42747
42748
42749
42731
42732
42733

FIG. 34



(a)

(b)

FIG. 35

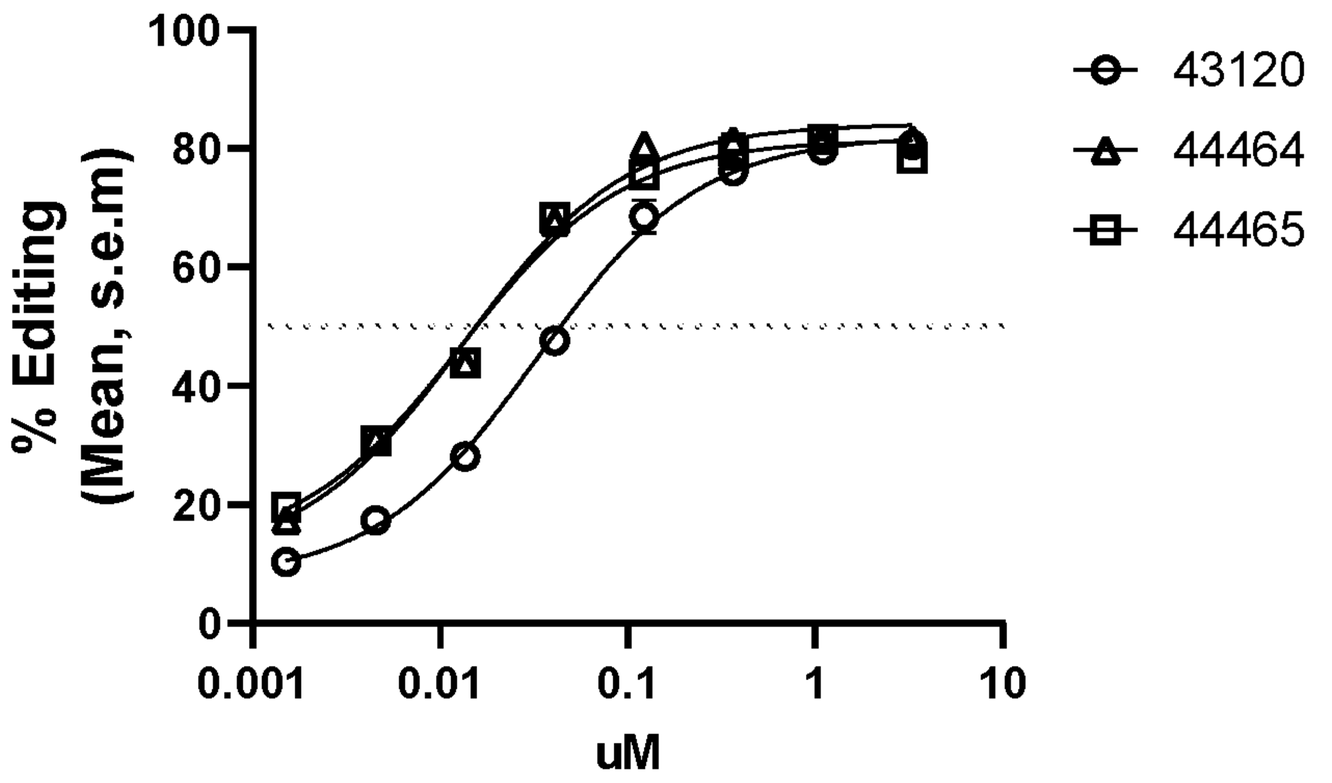


FIG. 36

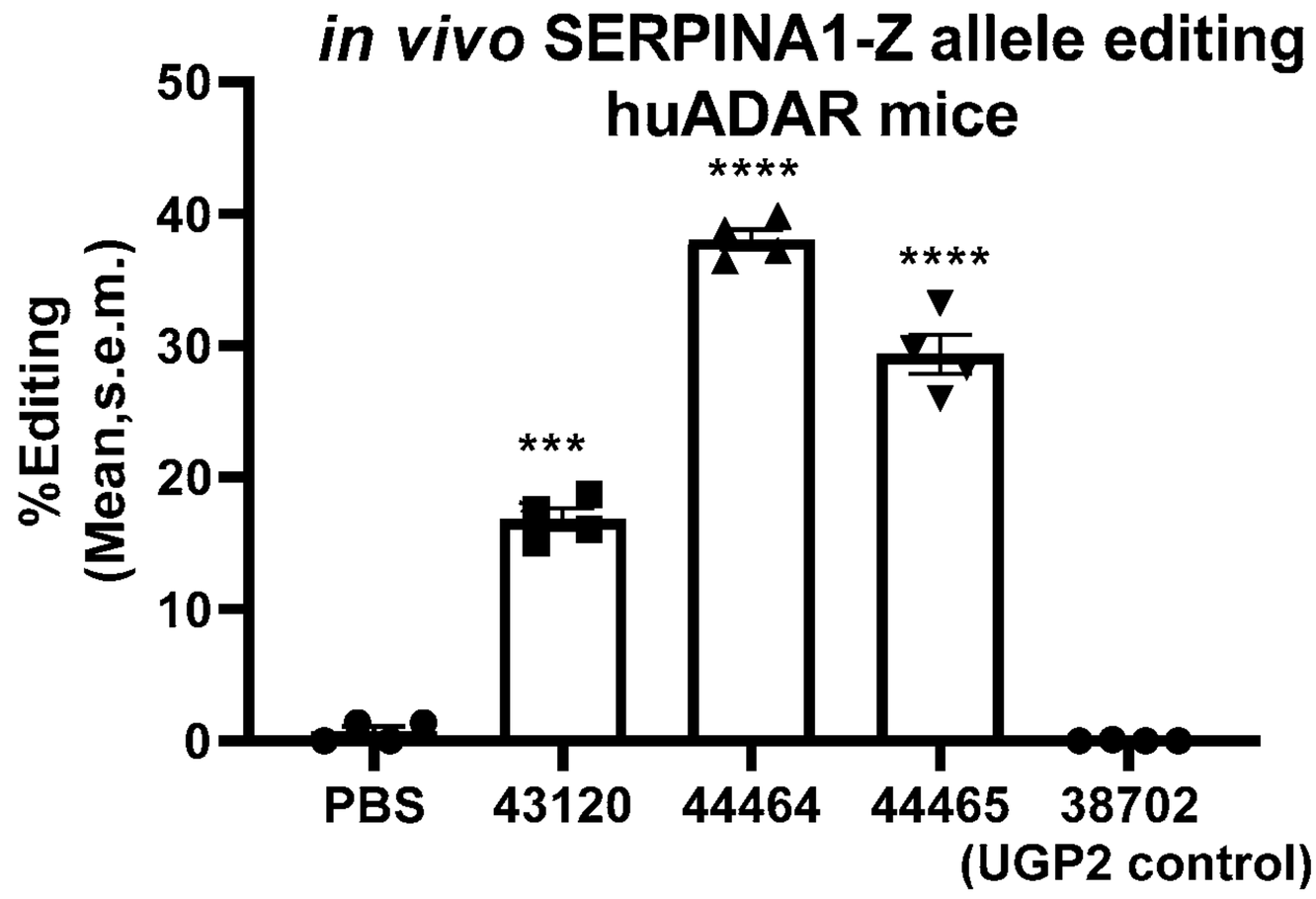


FIG. 37

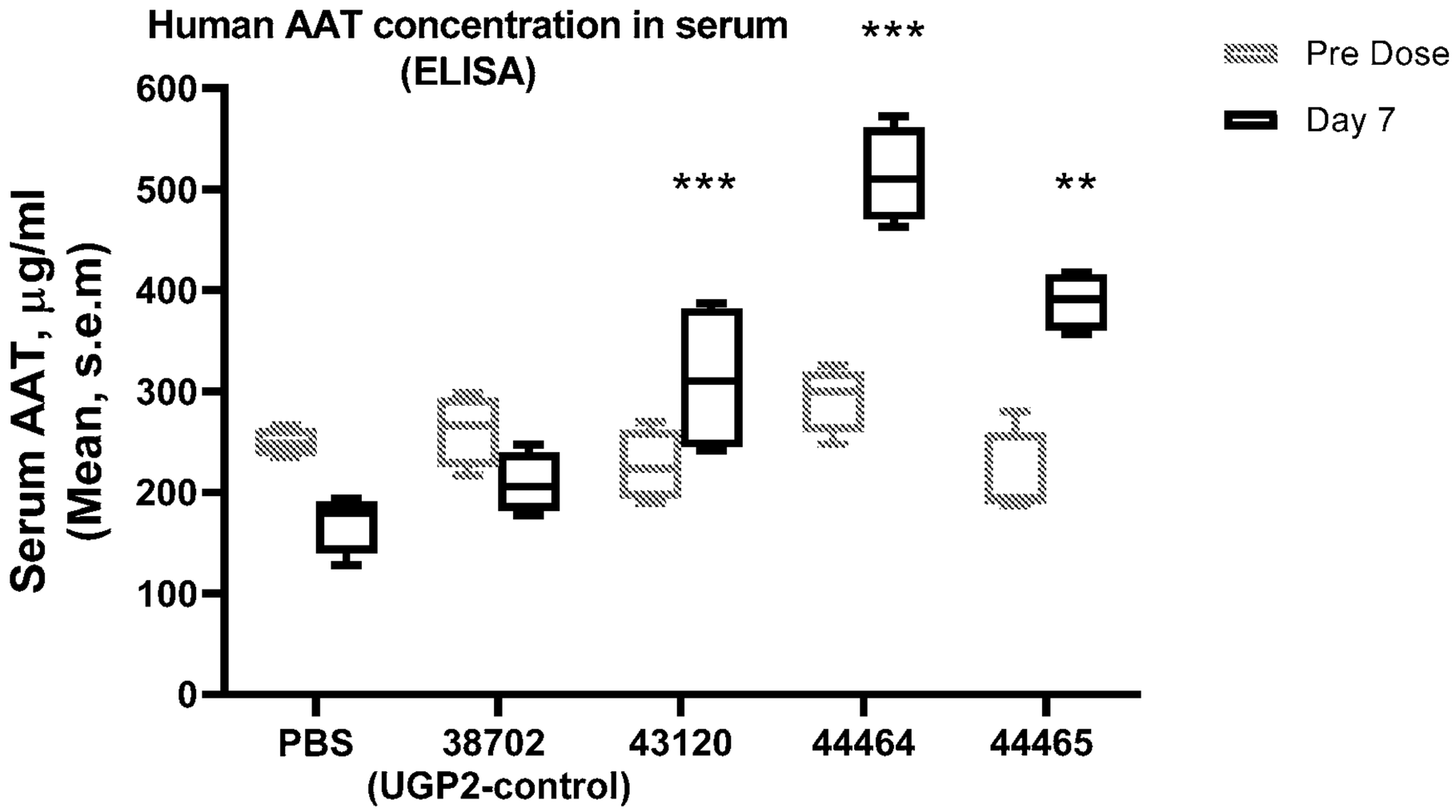


FIG. 38

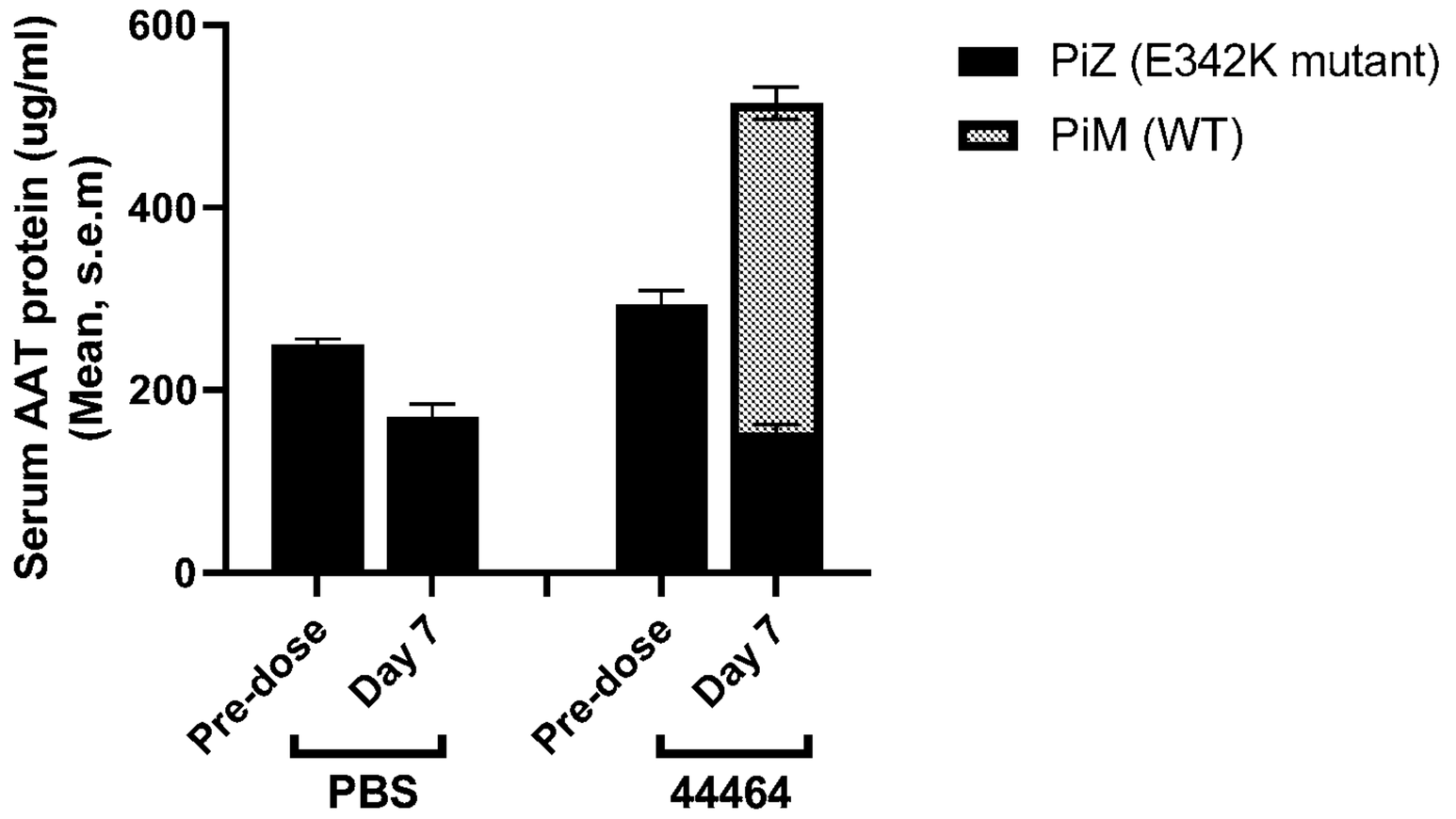


FIG. 39

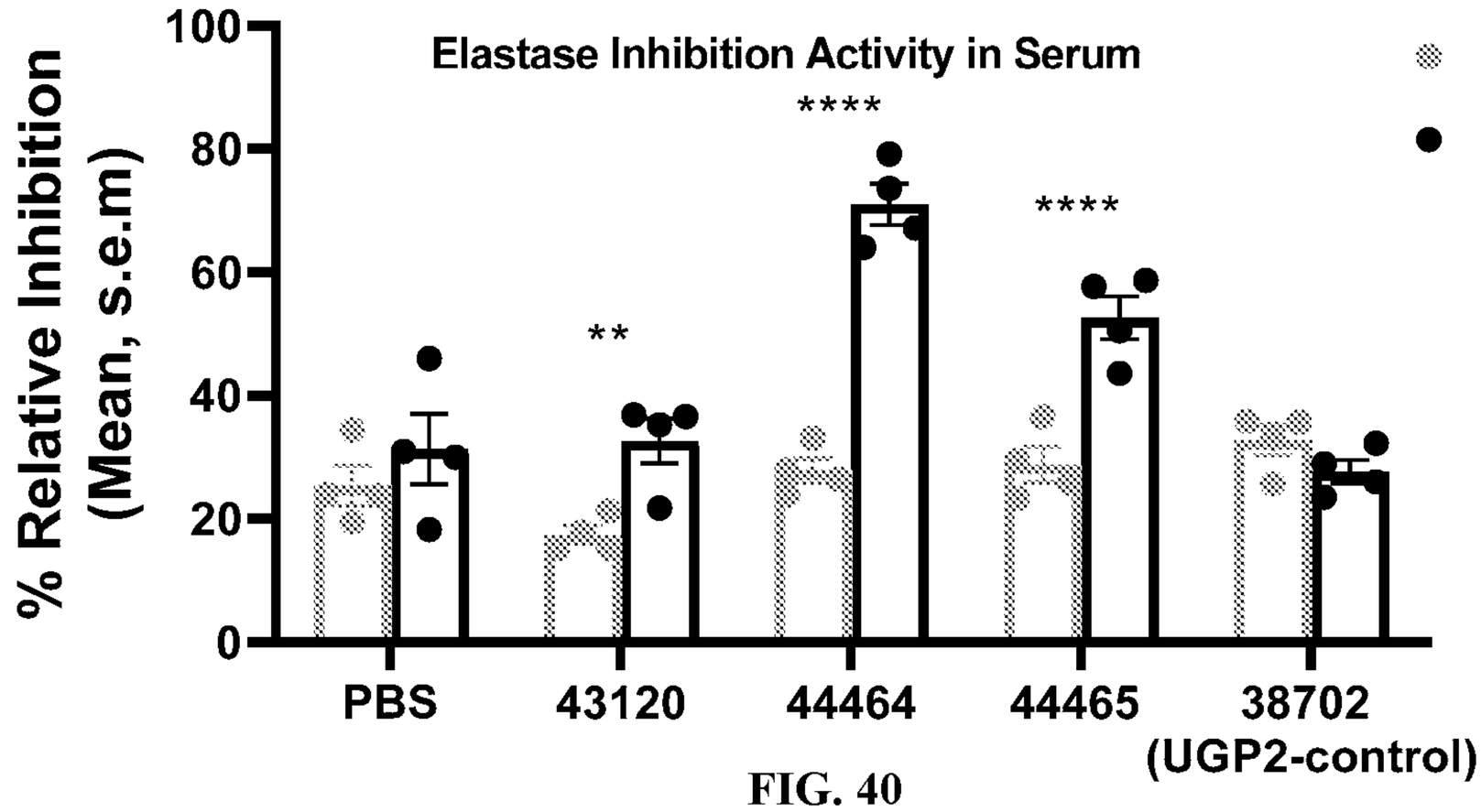
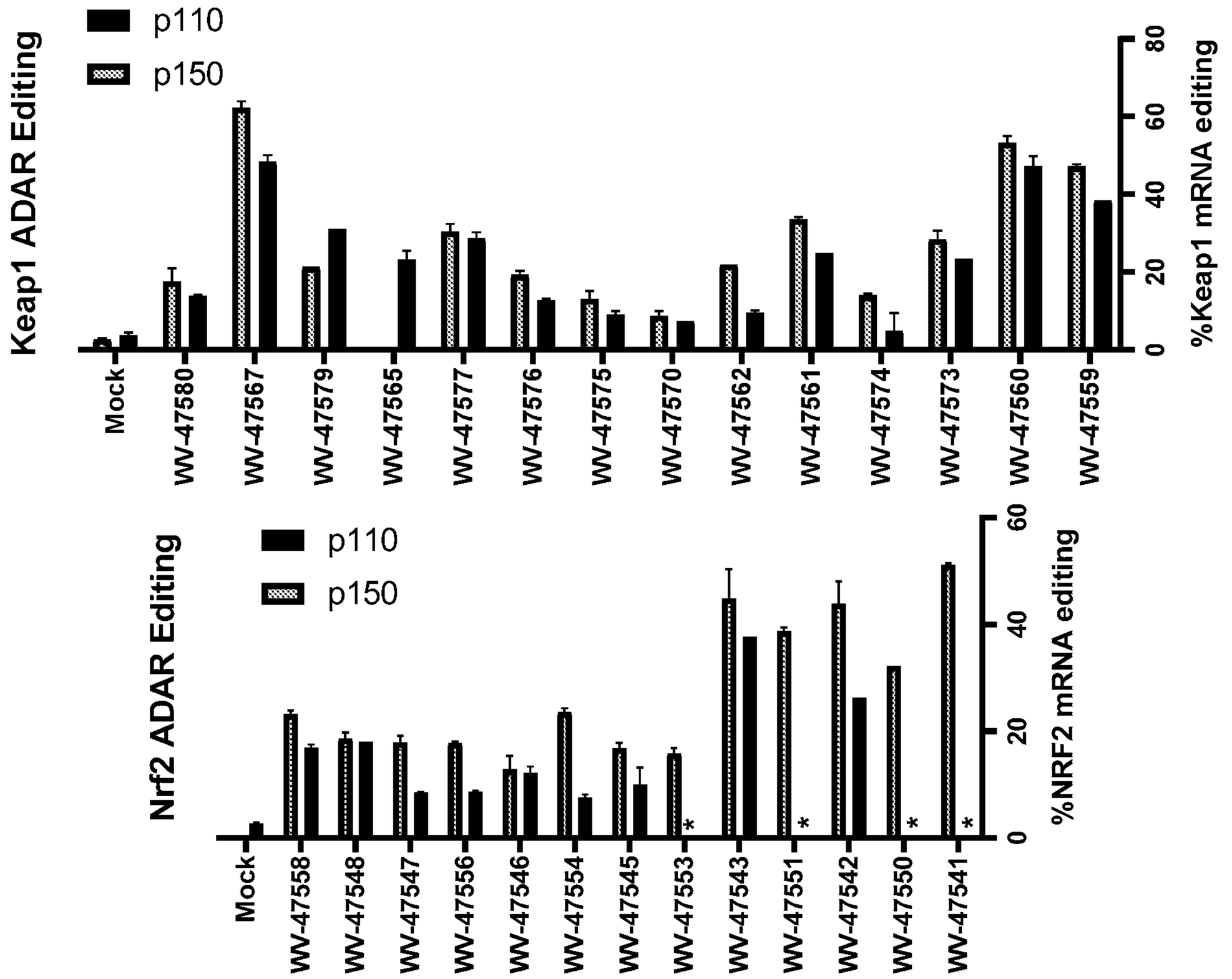
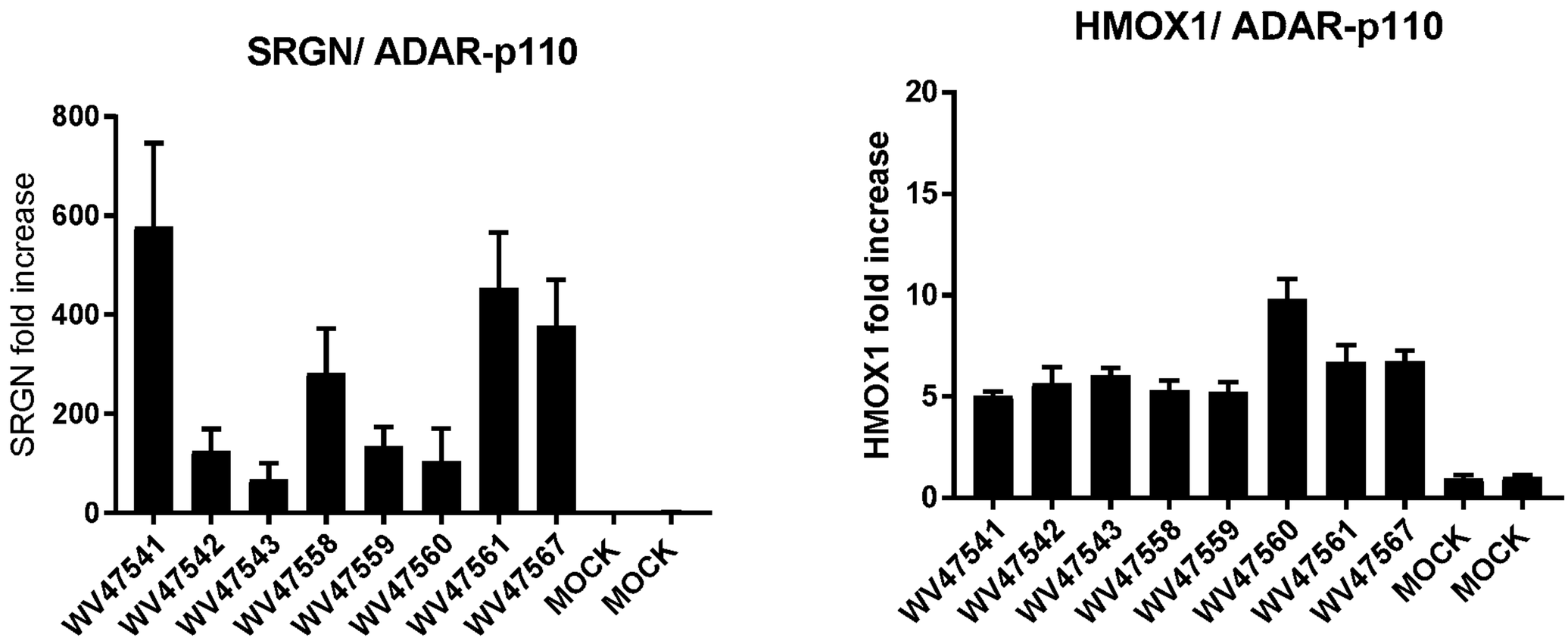


FIG. 40

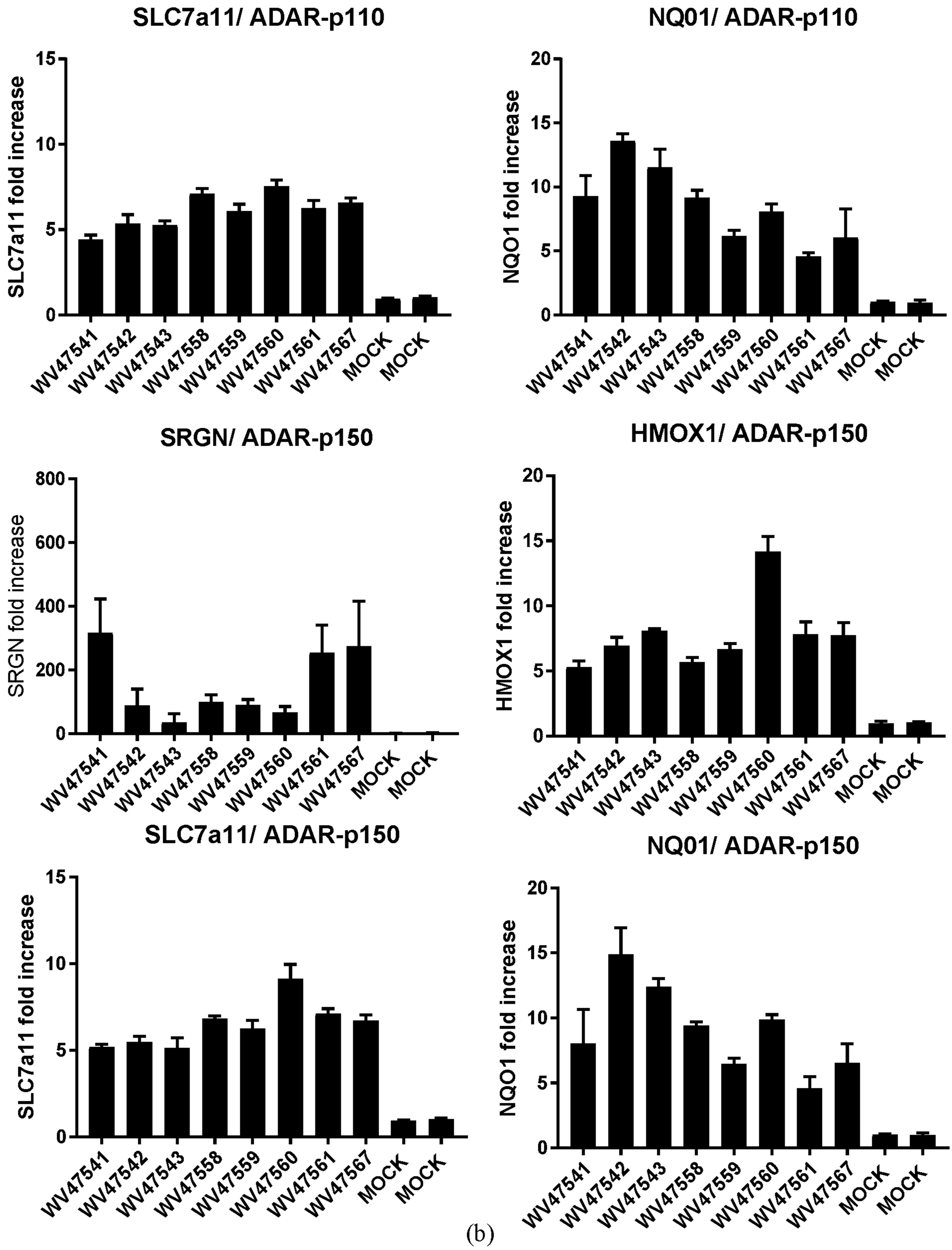

p110
p150
Keap1 ADAR Editing
%Keap1 mRNA editing
0
20
40
60
80
Mock
WV-47580
WV-47567
WV-47579
WV-47565
WV-47577
WV-47576
WV-47575
WV-47570
WV-47562
WV-47561
WV-47574
WV-47573
WV-47560
WV-47559
Nrf2 ADAR Editing
p110
p150
%NRF2 mRNA editing
0
20
40
60
*
Mock
WV-47558
WV-47548
WV-47547
WV-47556
WV-47546
WV-47554
WV-47545
WV-47553
WV-47543
WV-47551
WV-47542
WV-47550
WV-47541

(a)


SRGN/ ADAR-p110
SRGN fold increase
0
200
400
600
800
WV47541
WV47542
WV47543
WV47558
WV47559
WV47560
WV47561
WV47567
MOCK
MOCK
HMOX1/ ADAR-p110
HMOX1 fold increase
0
5
10
15
20
WV47541
WV47542
WV47543
WV47558
WV47559
WV47560
WV47561
WV47567
MOCK
MOCK

(b)

FIG. 41



(b)

FIG. 41
(CONTINUED)

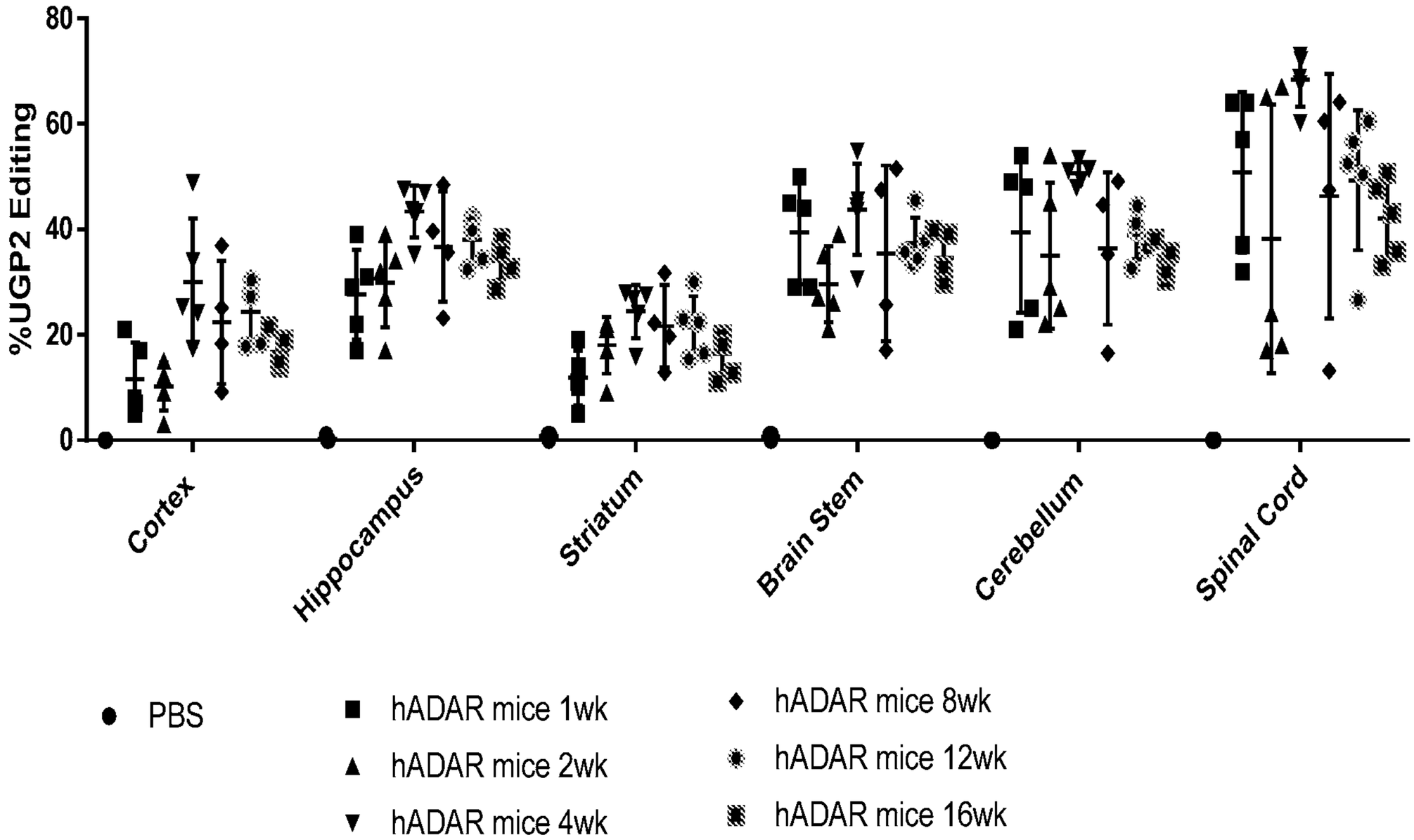


FIG. 42

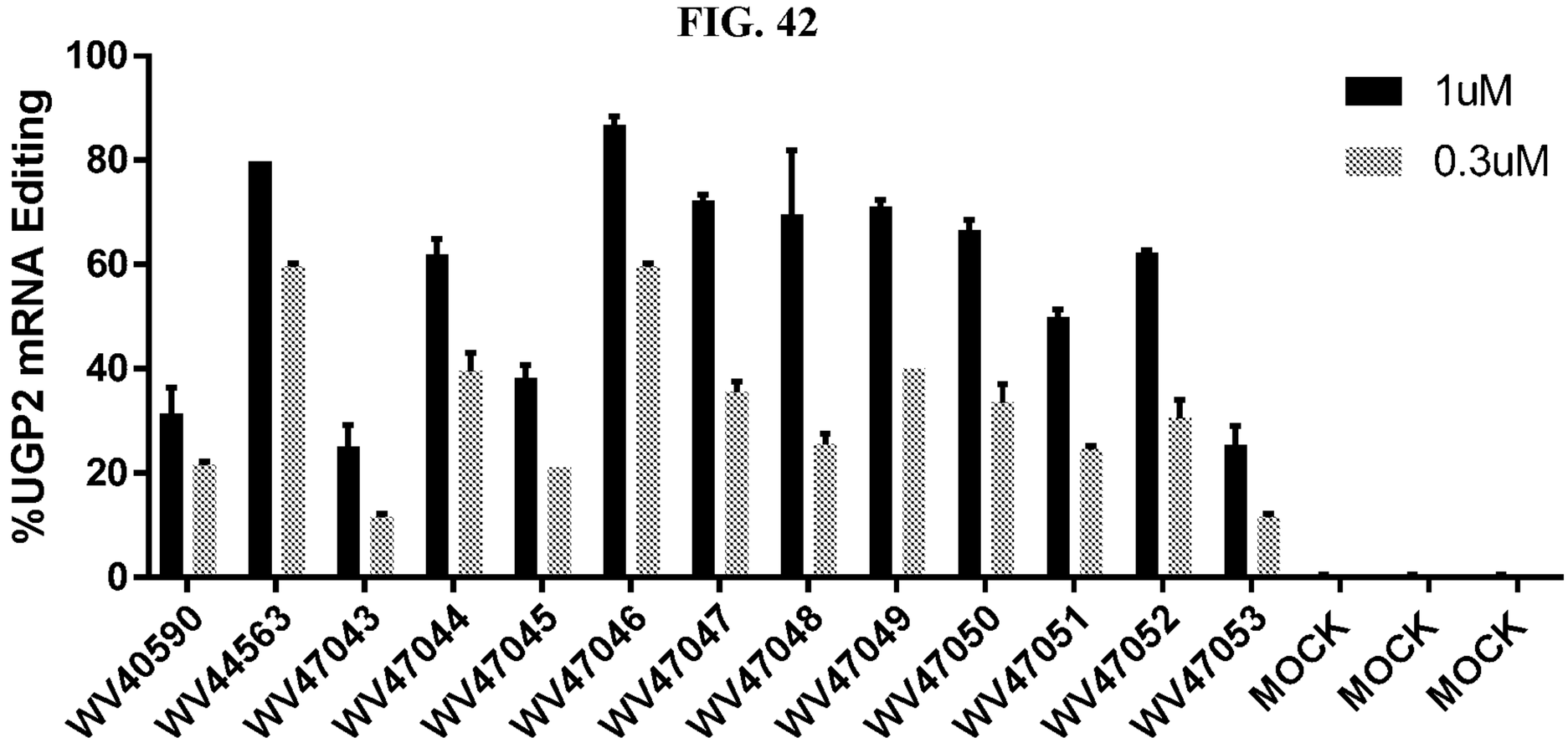


FIG. 43

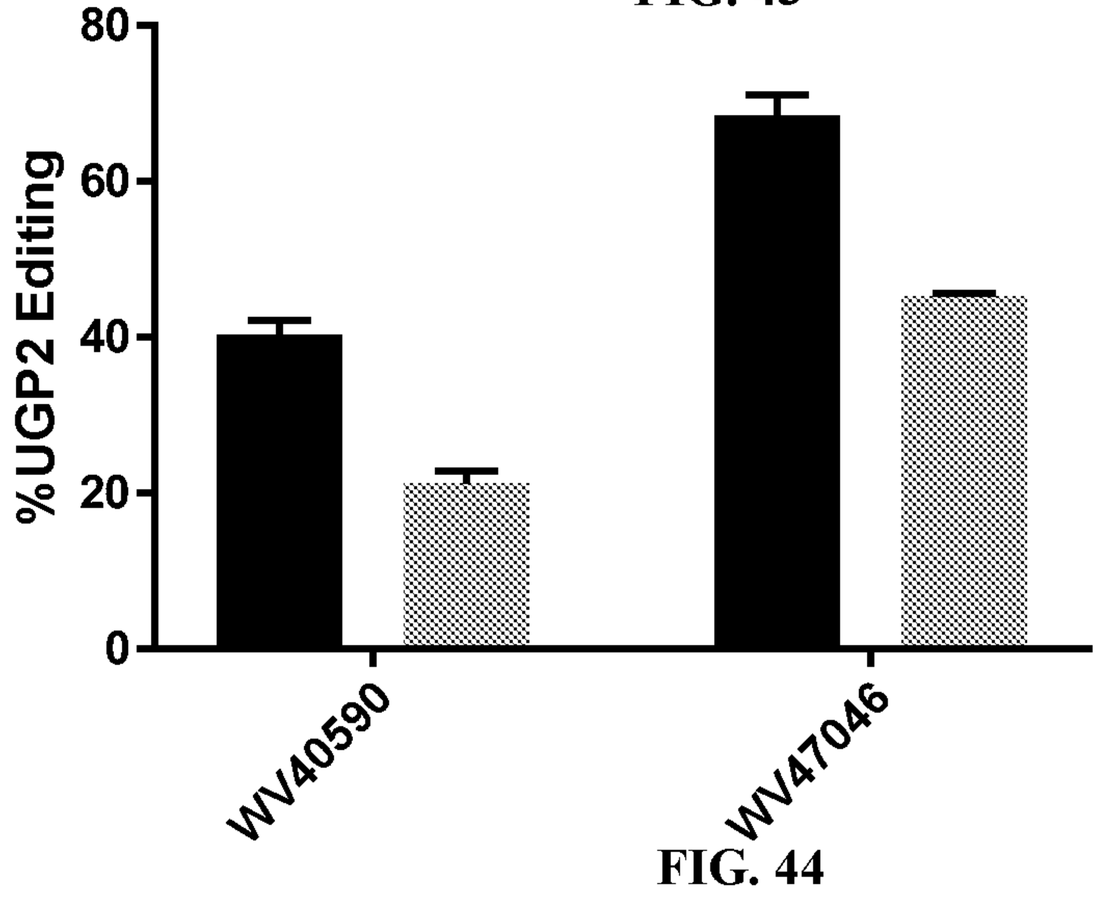


FIG. 44

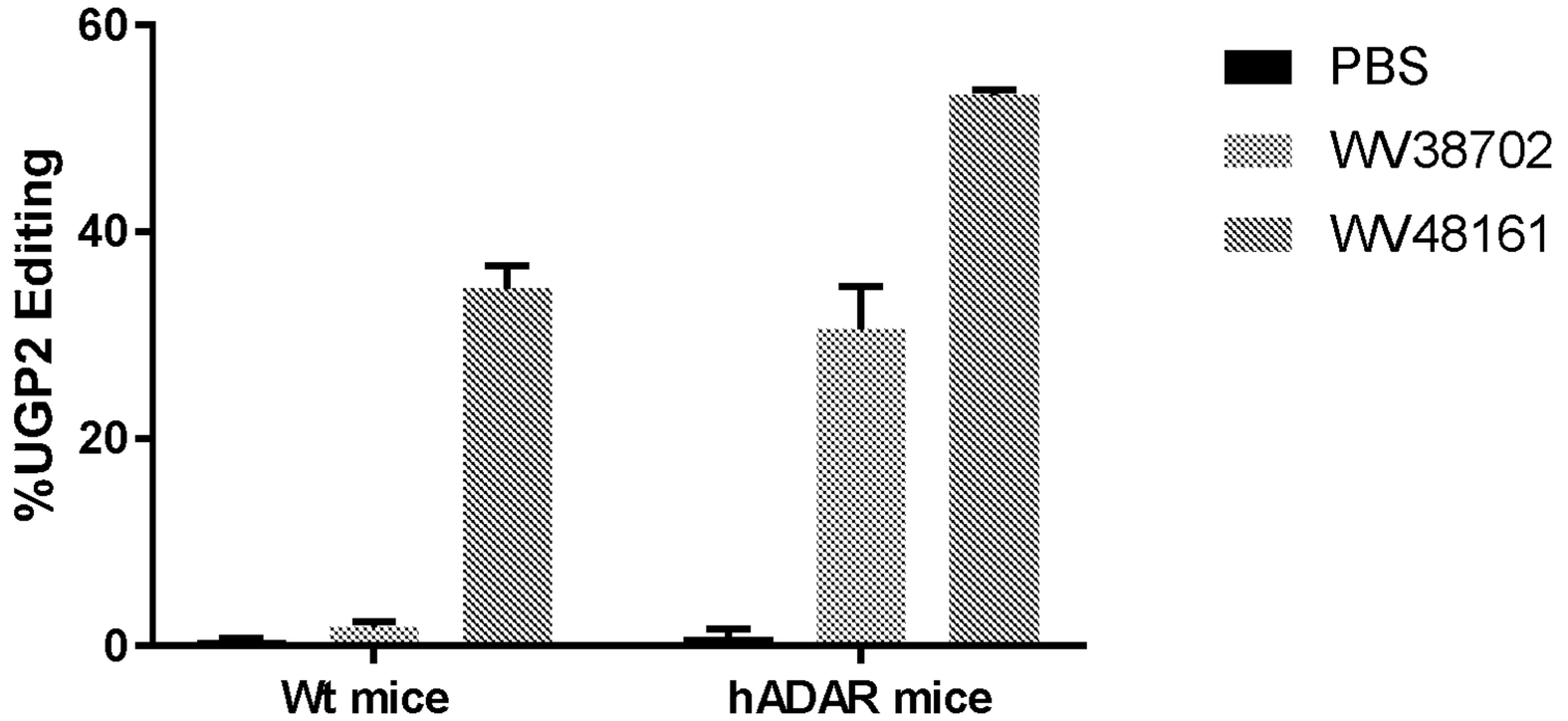


FIG. 45

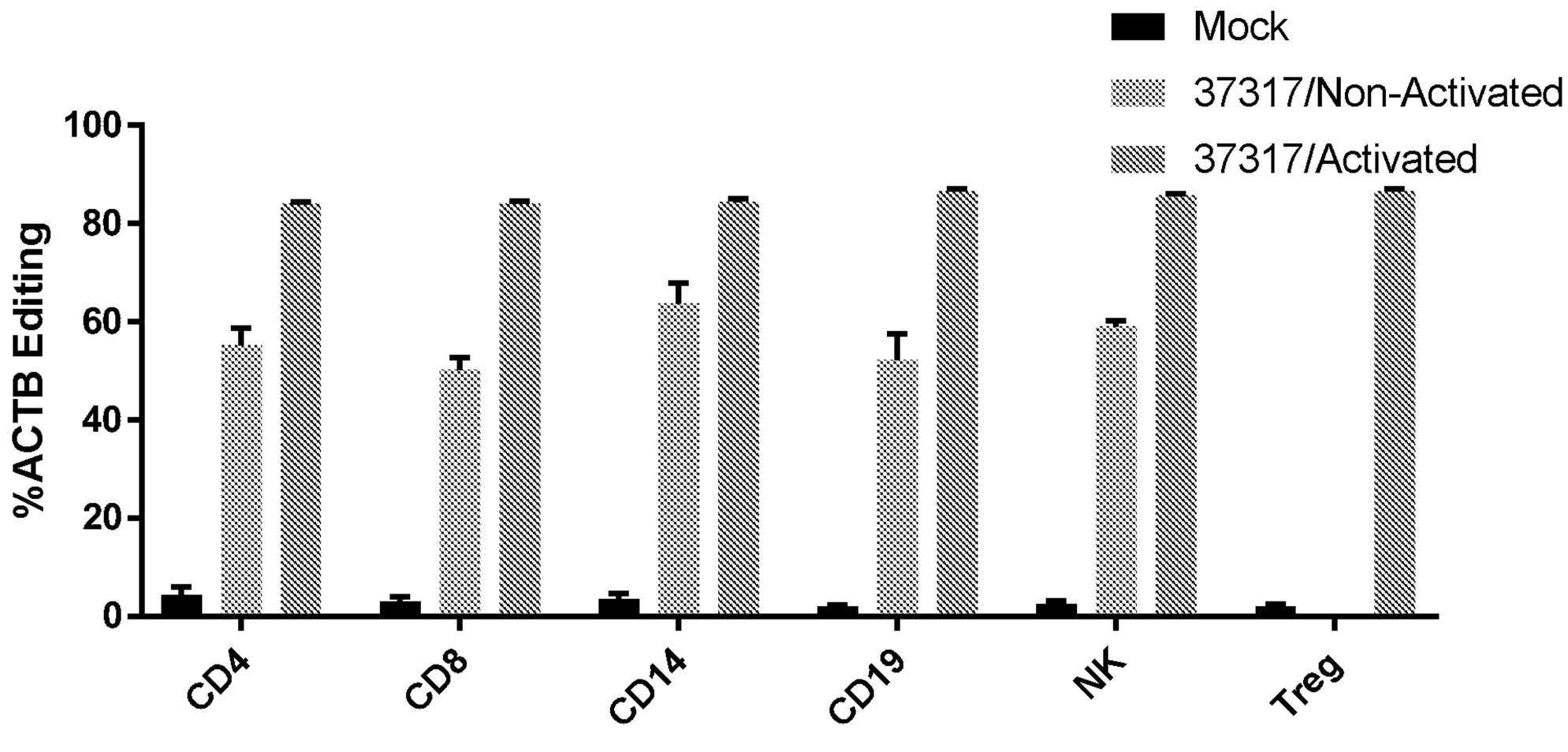


FIG. 46

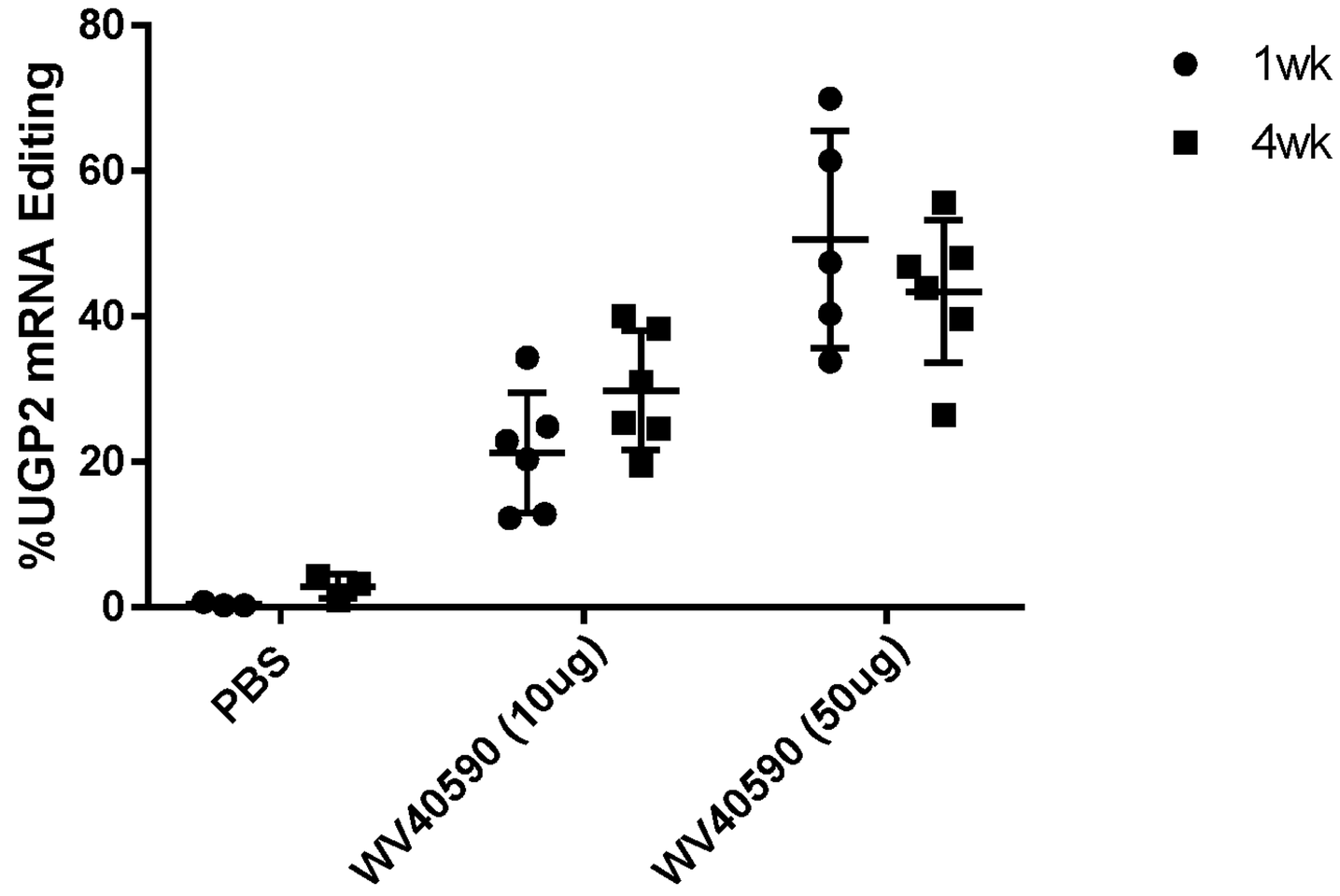
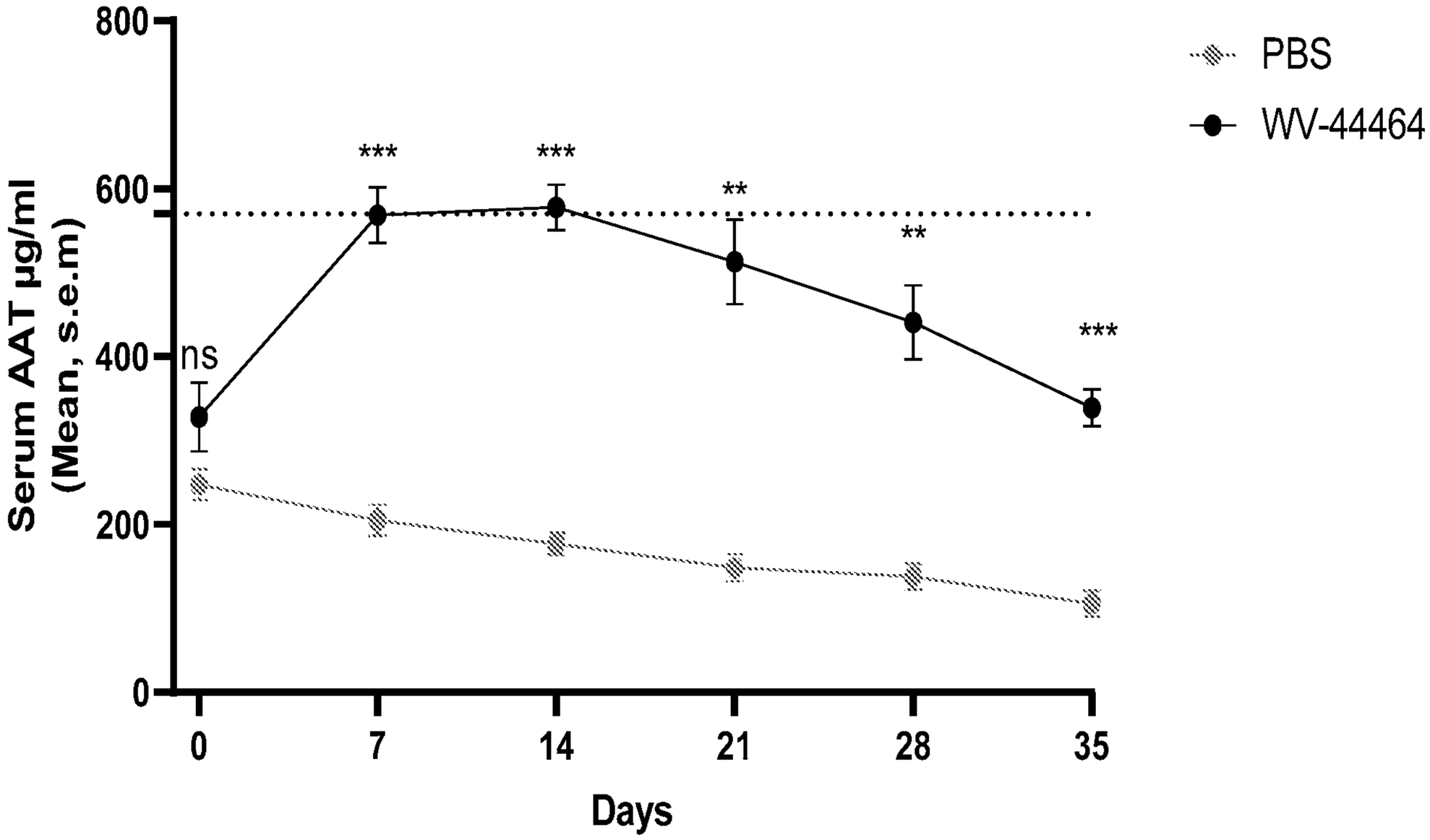
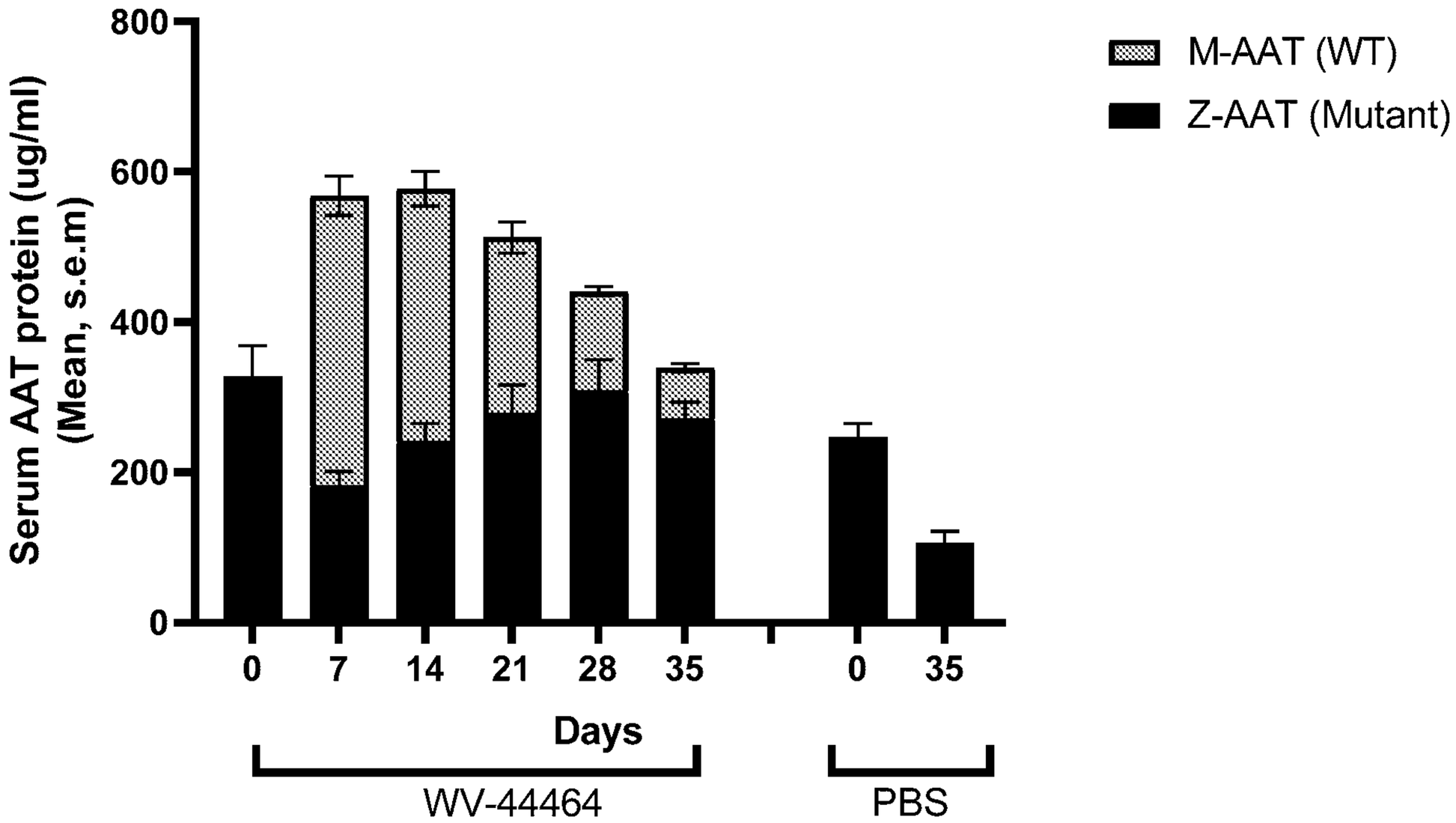


FIG. 47


PBS
WV-44464
Serum AAT µg/ml (Mean, s.e.m)
800
600
400
200
0
ns
***
***
**
**
***
0
7
14
21
28
35
Days

(a)


M-AAT (WT)
Z-AAT (Mutant)
Serum AAT protein (ug/ml) (Mean, s.e.m)
800
600
400
200
0
0
7
14
21
28
35
0
35
Days
WV-44464
PBS

(b)

FIG. 48

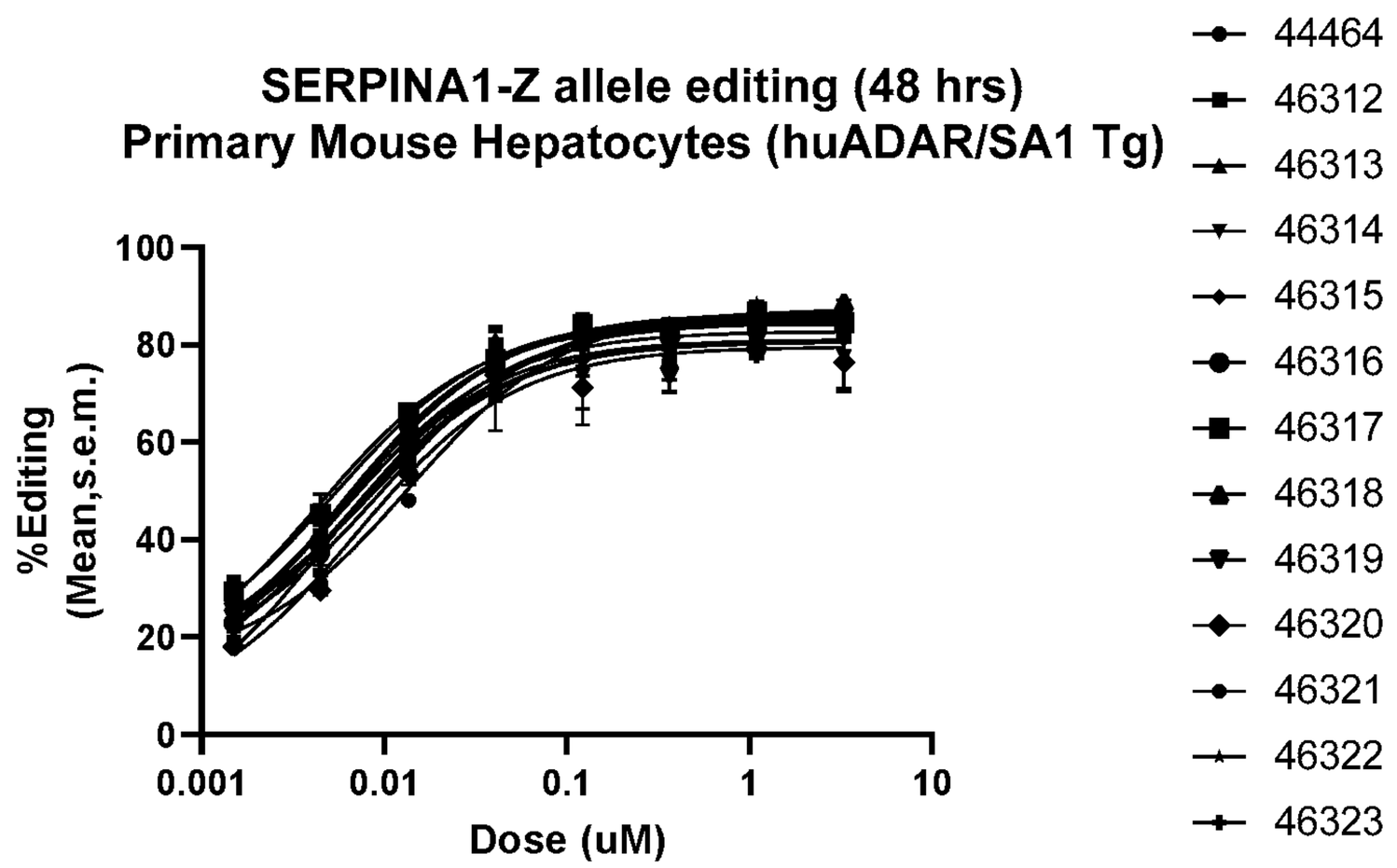


FIG. 49

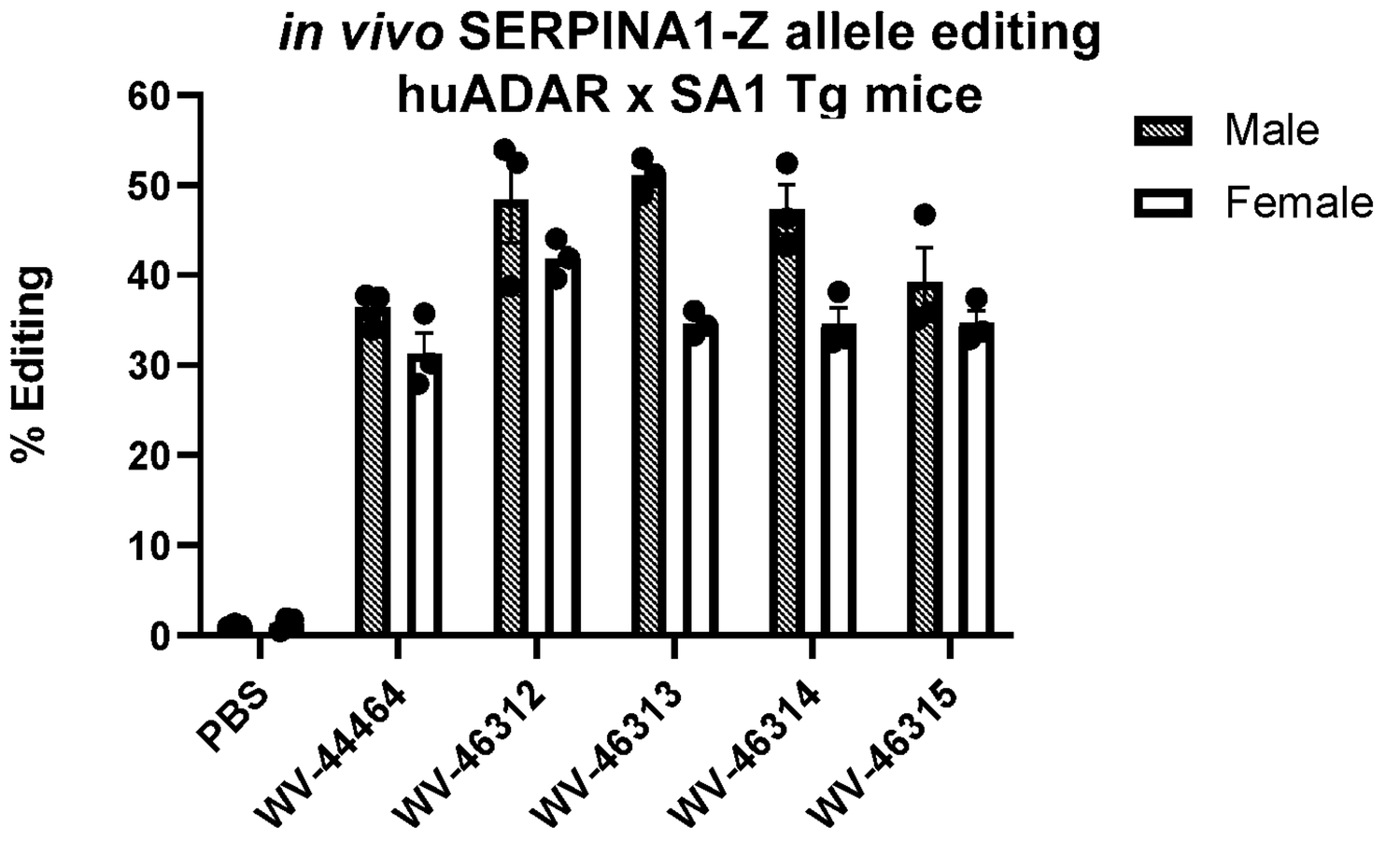


FIG. 50

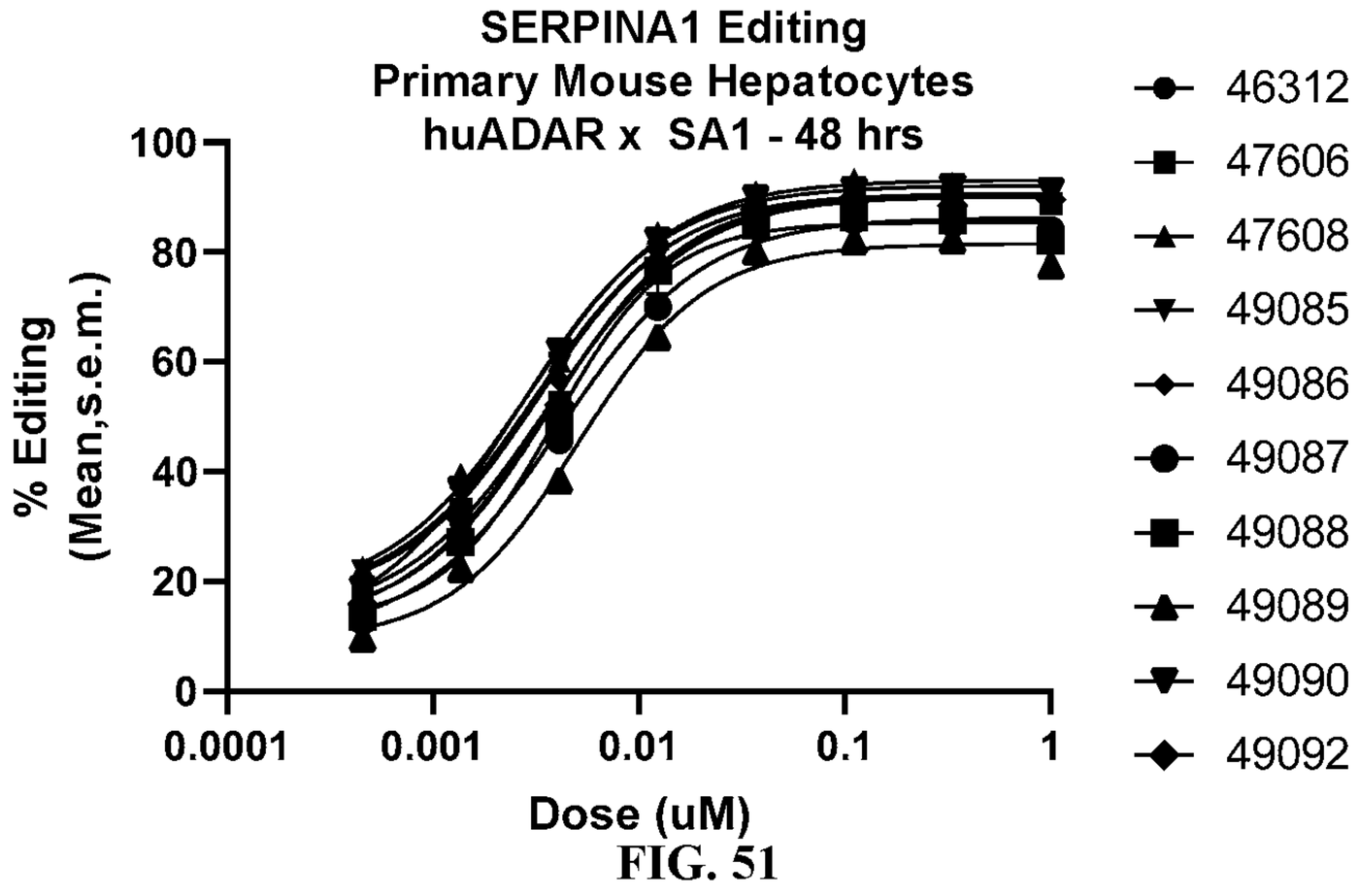


FIG. 51

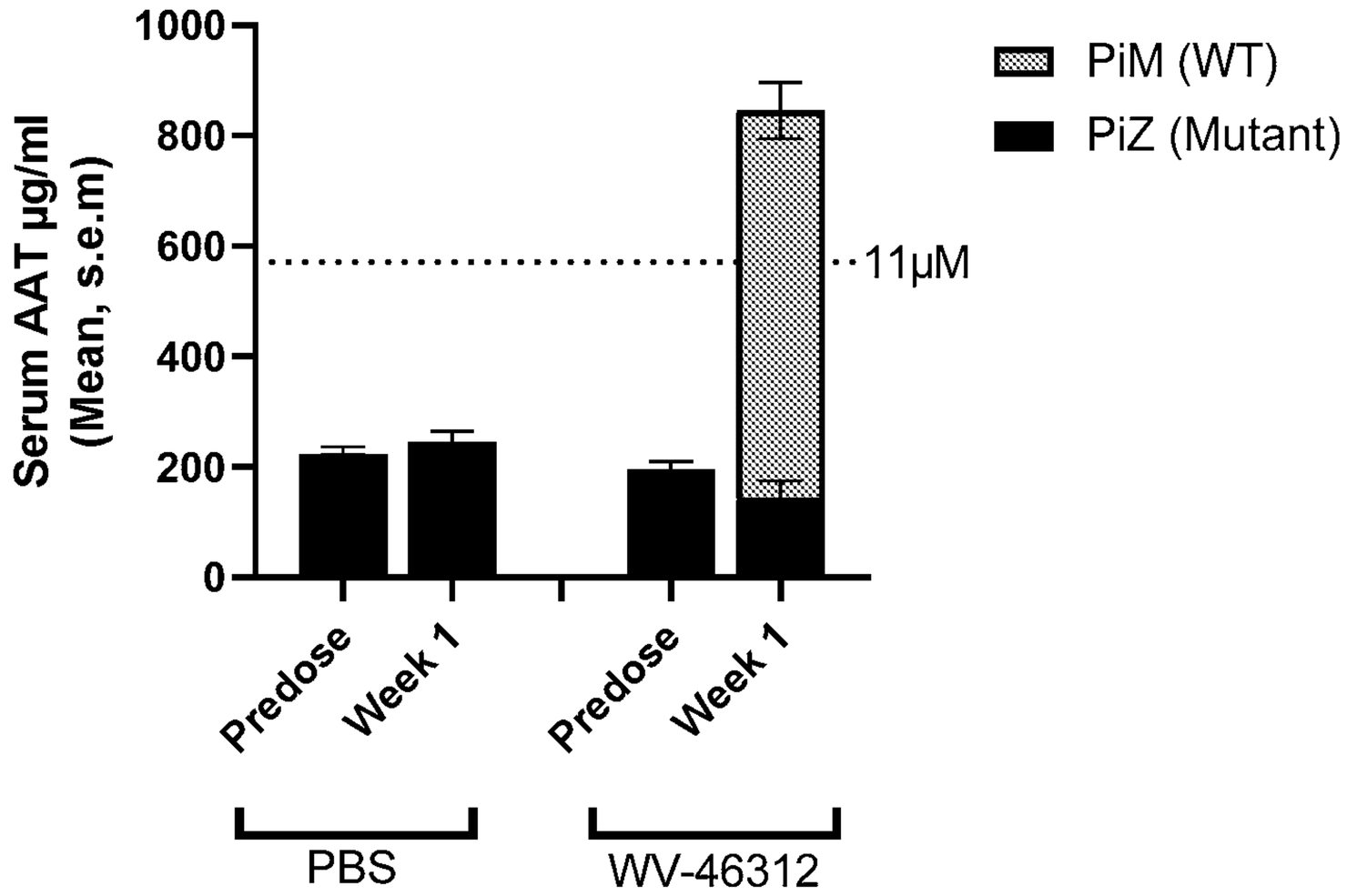


FIG. 52

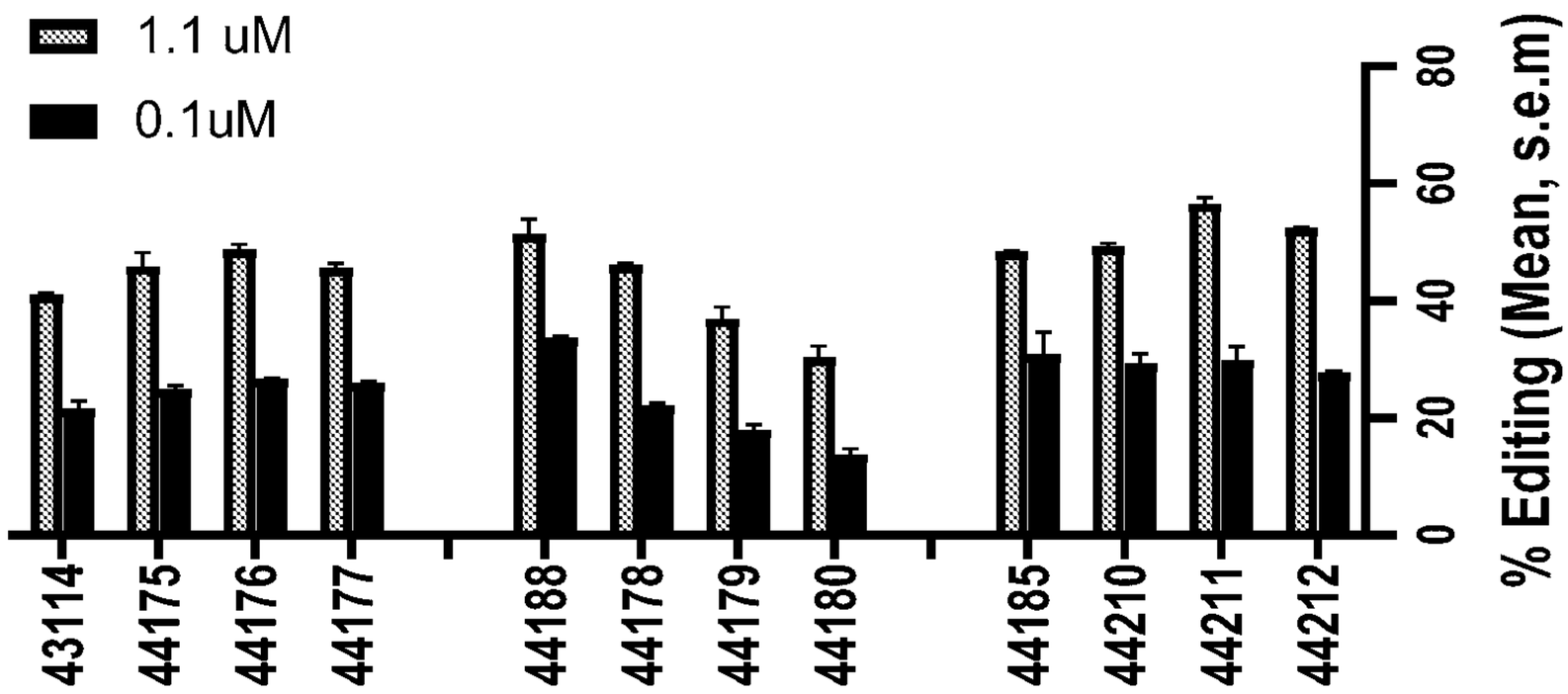


FIG. 53

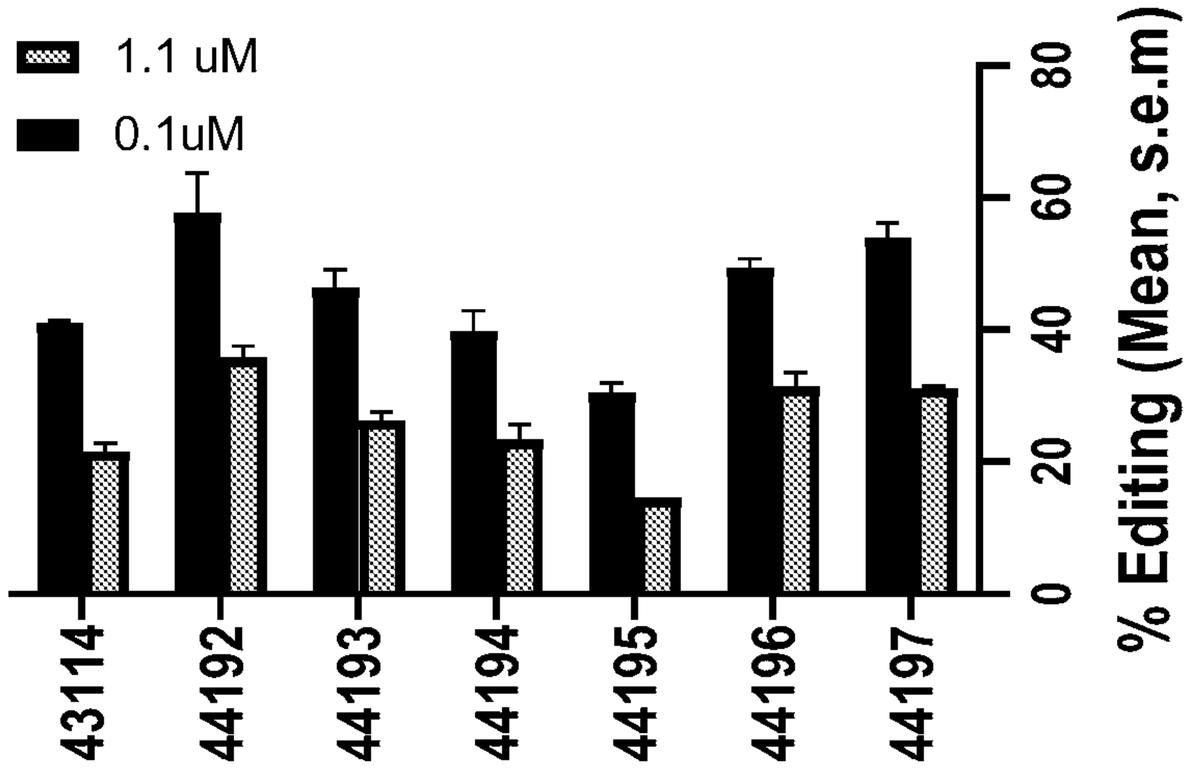


FIG. 54

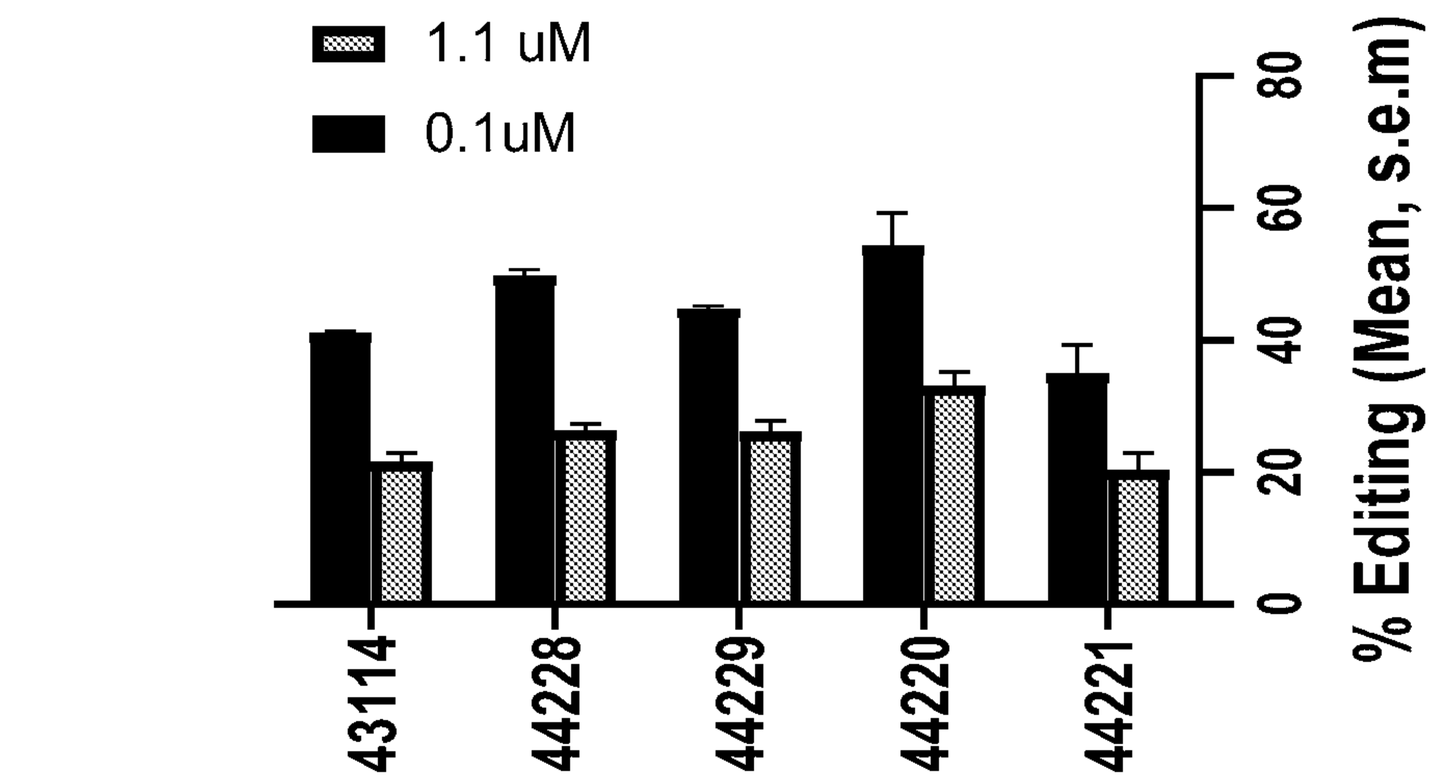


FIG. 55

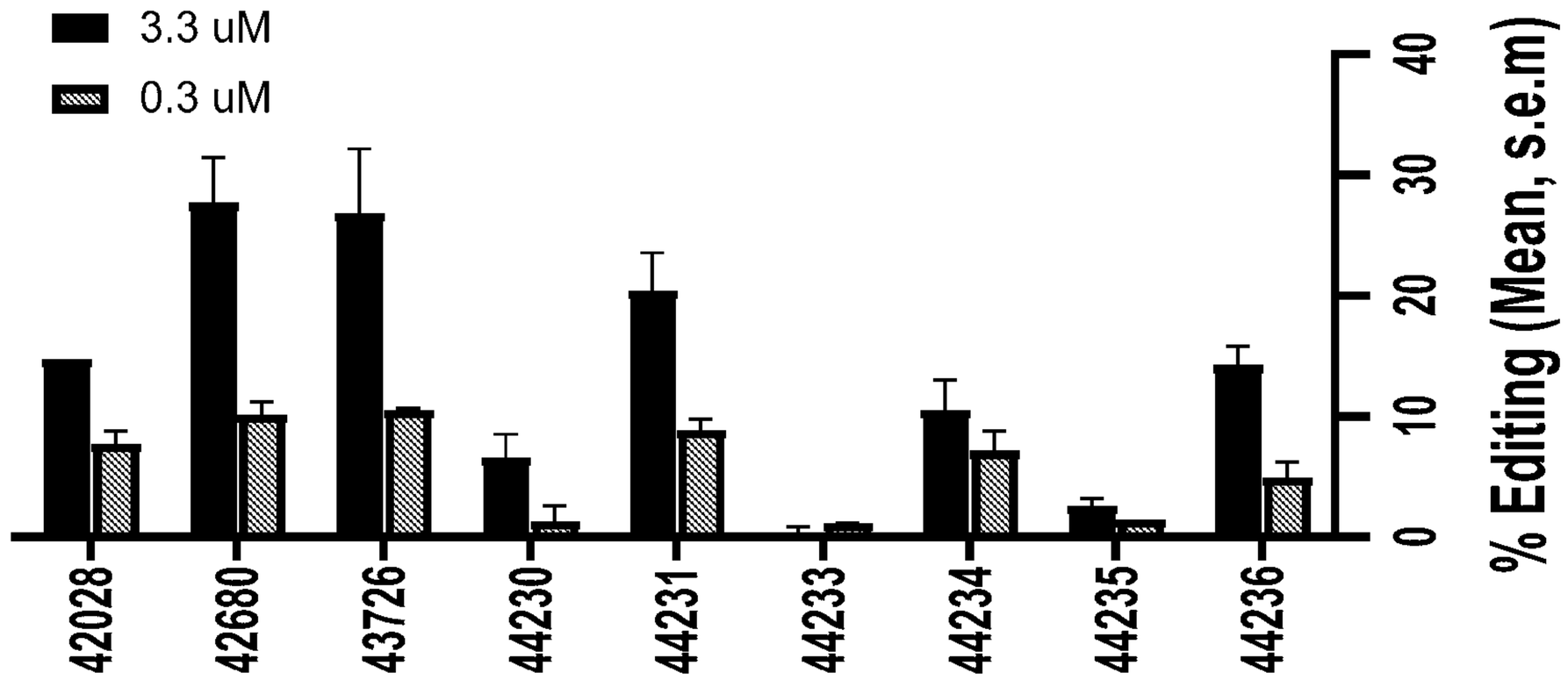


FIG. 56

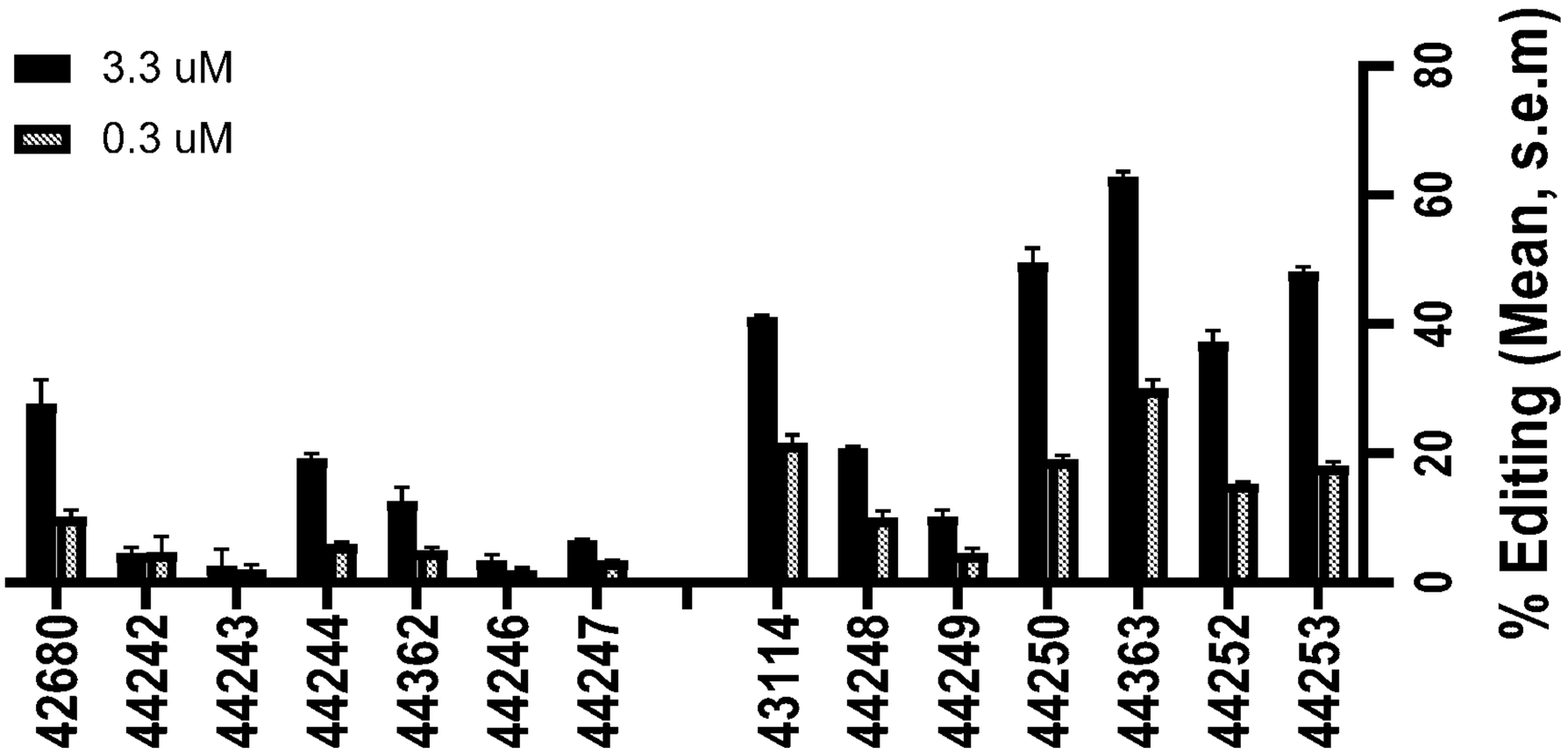


FIG. 57

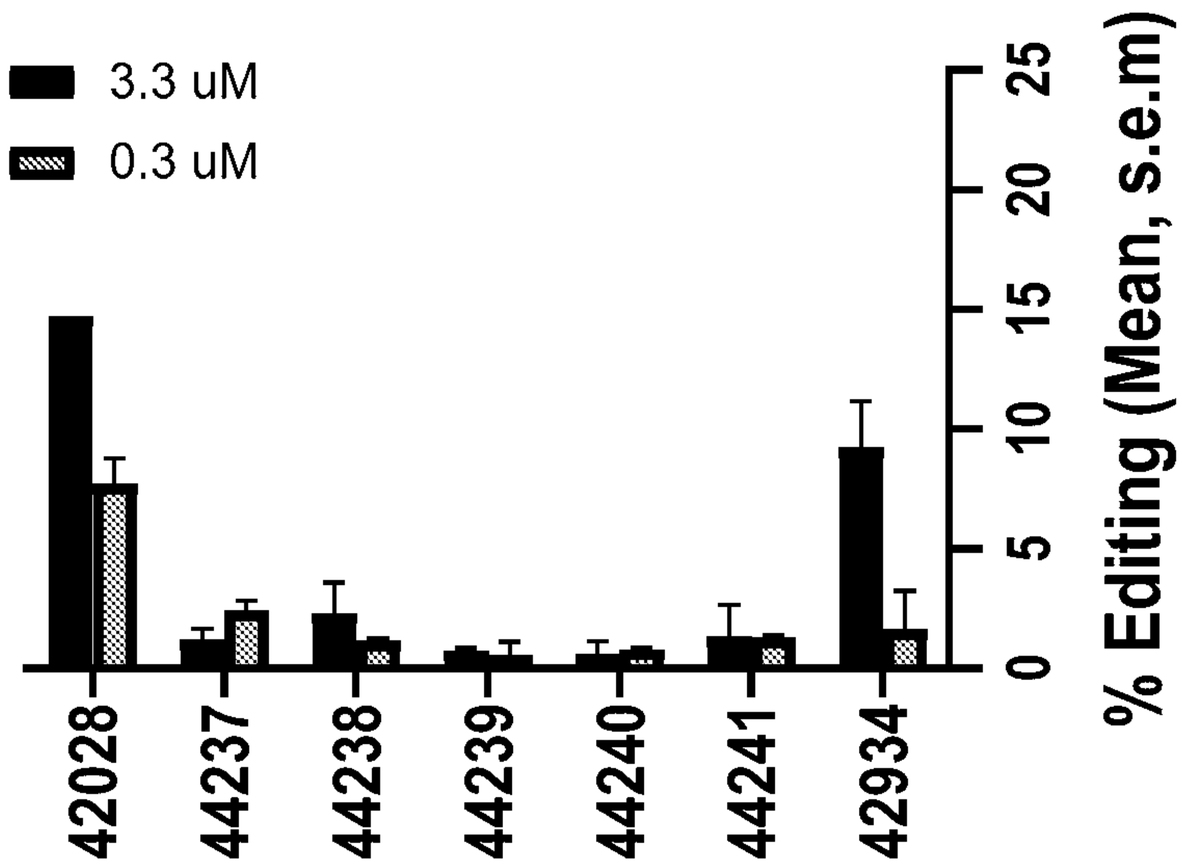


FIG. 58

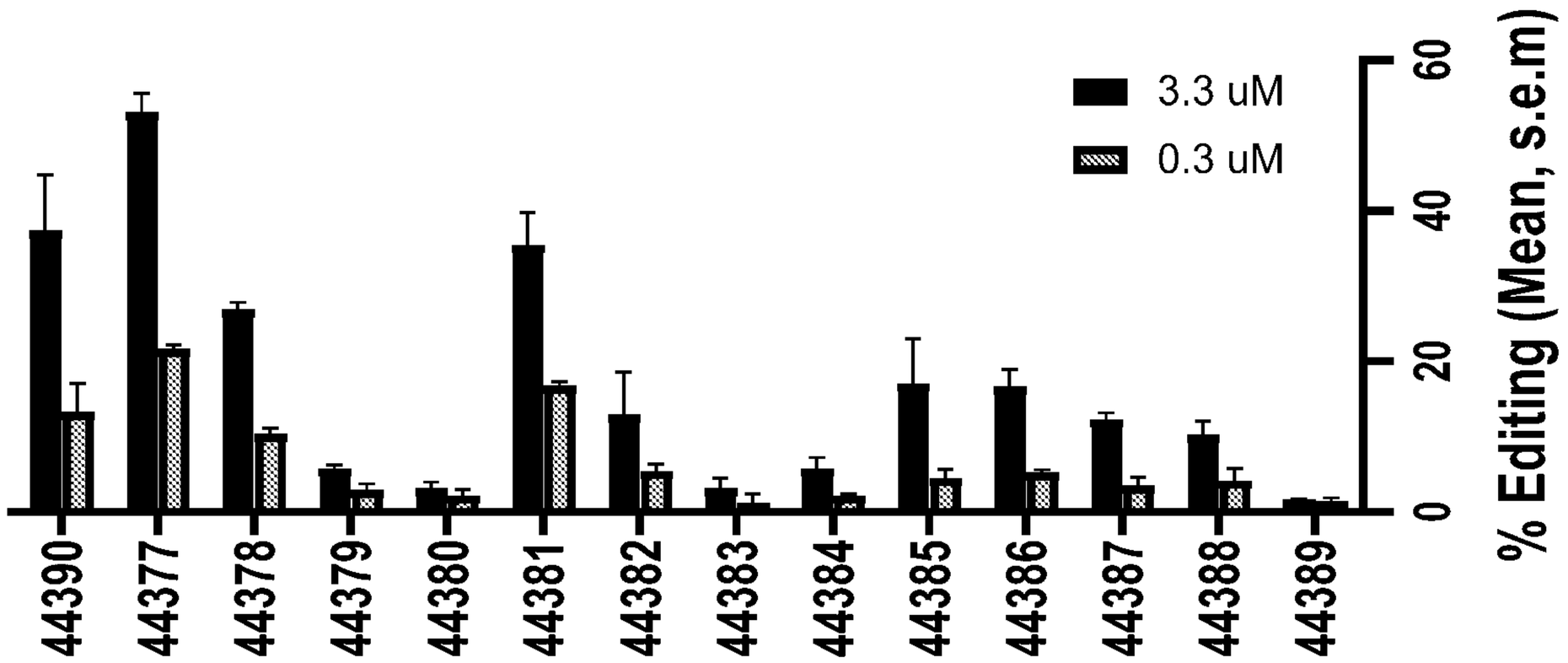


FIG. 59

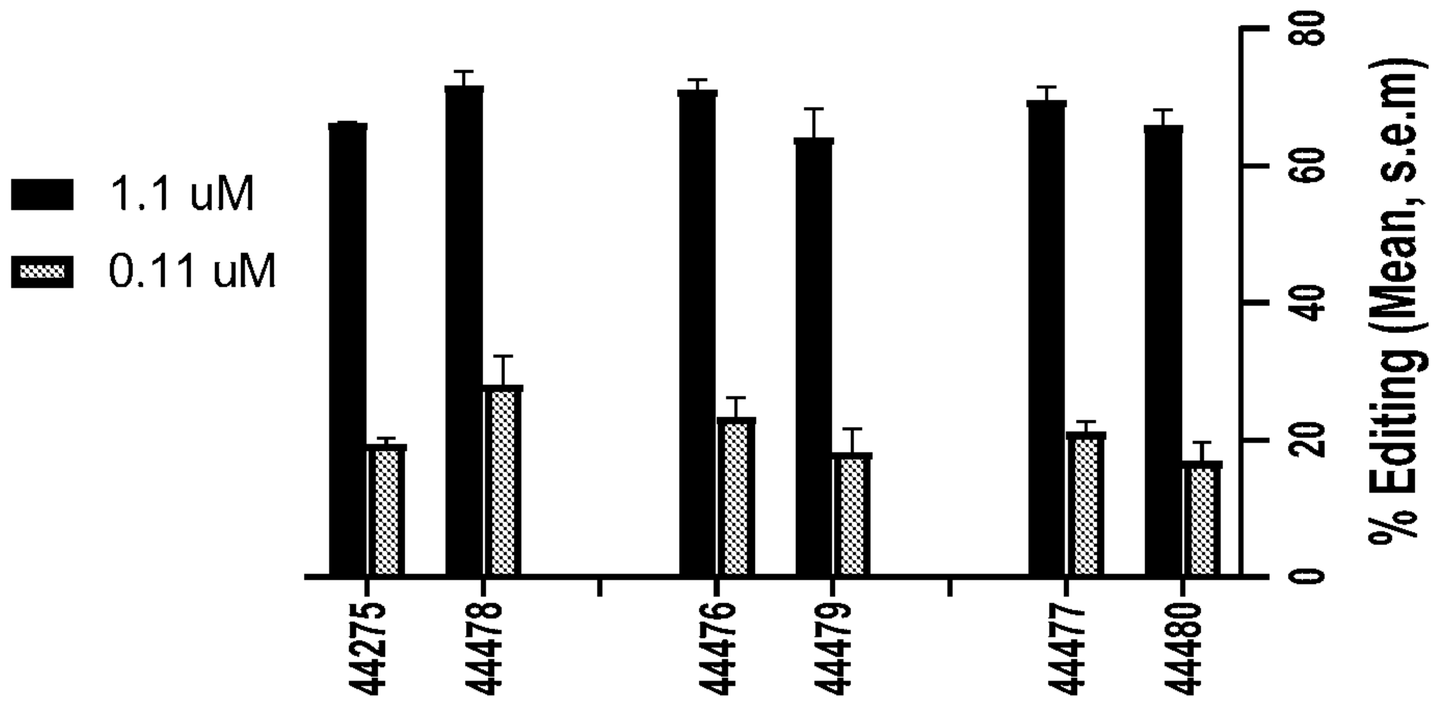


FIG. 60

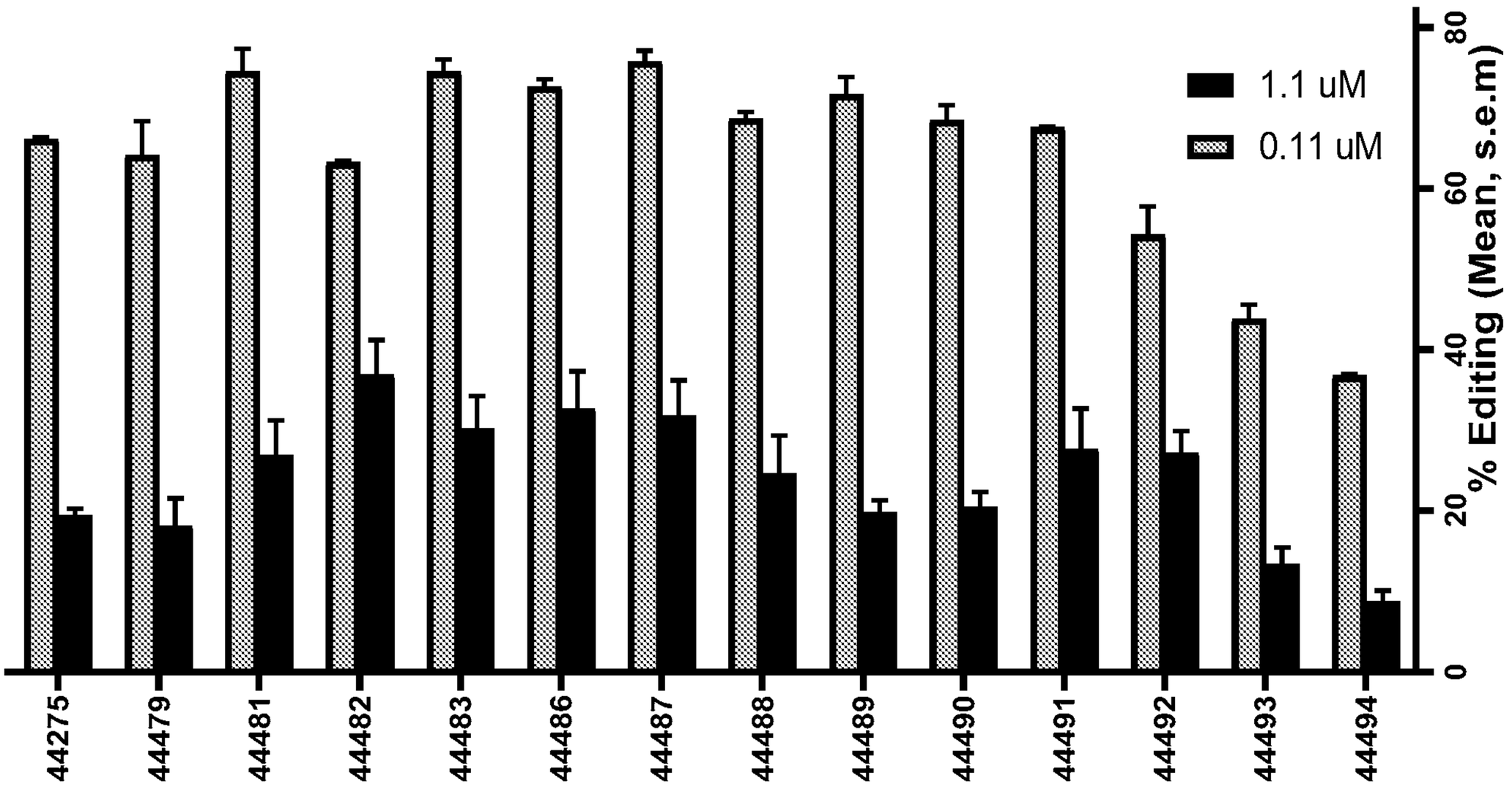


FIG. 61

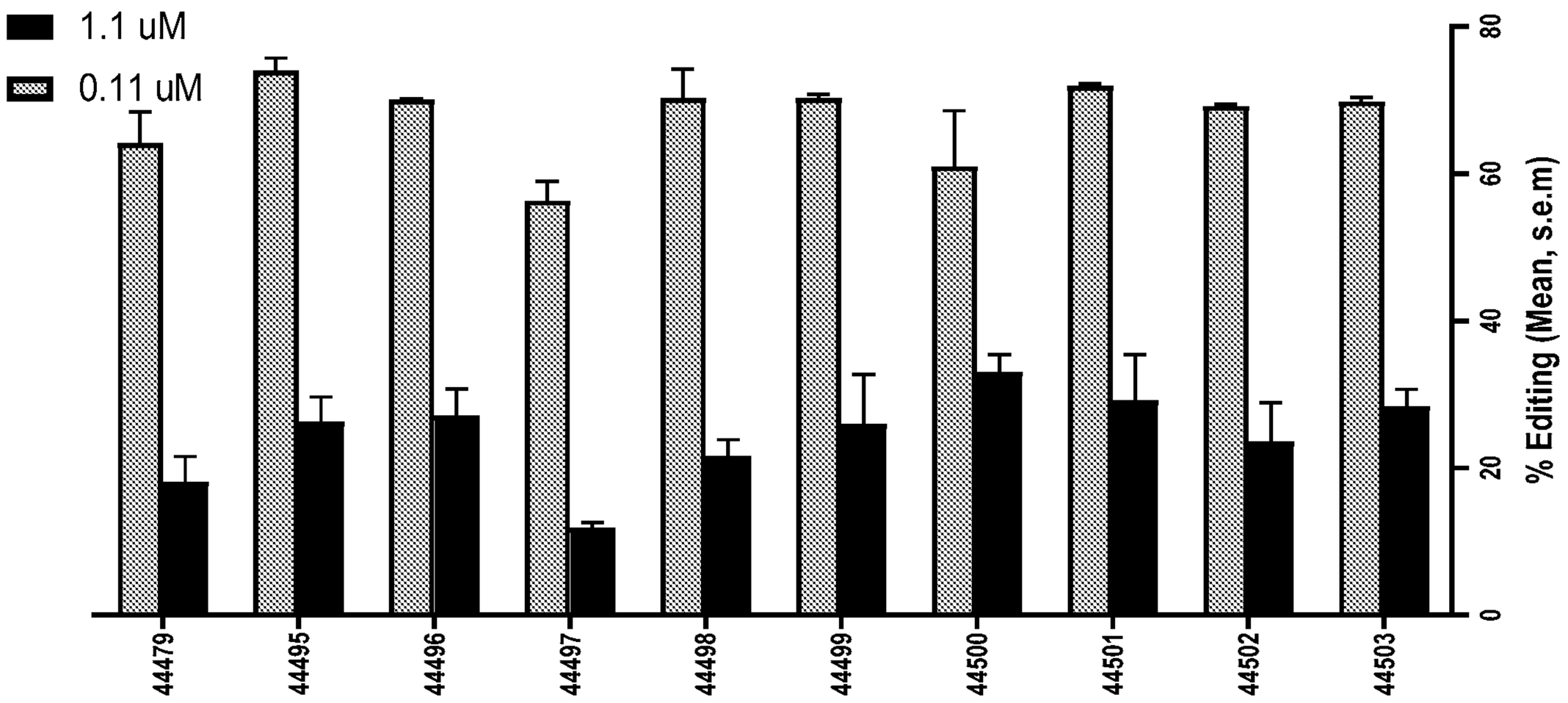


FIG. 62

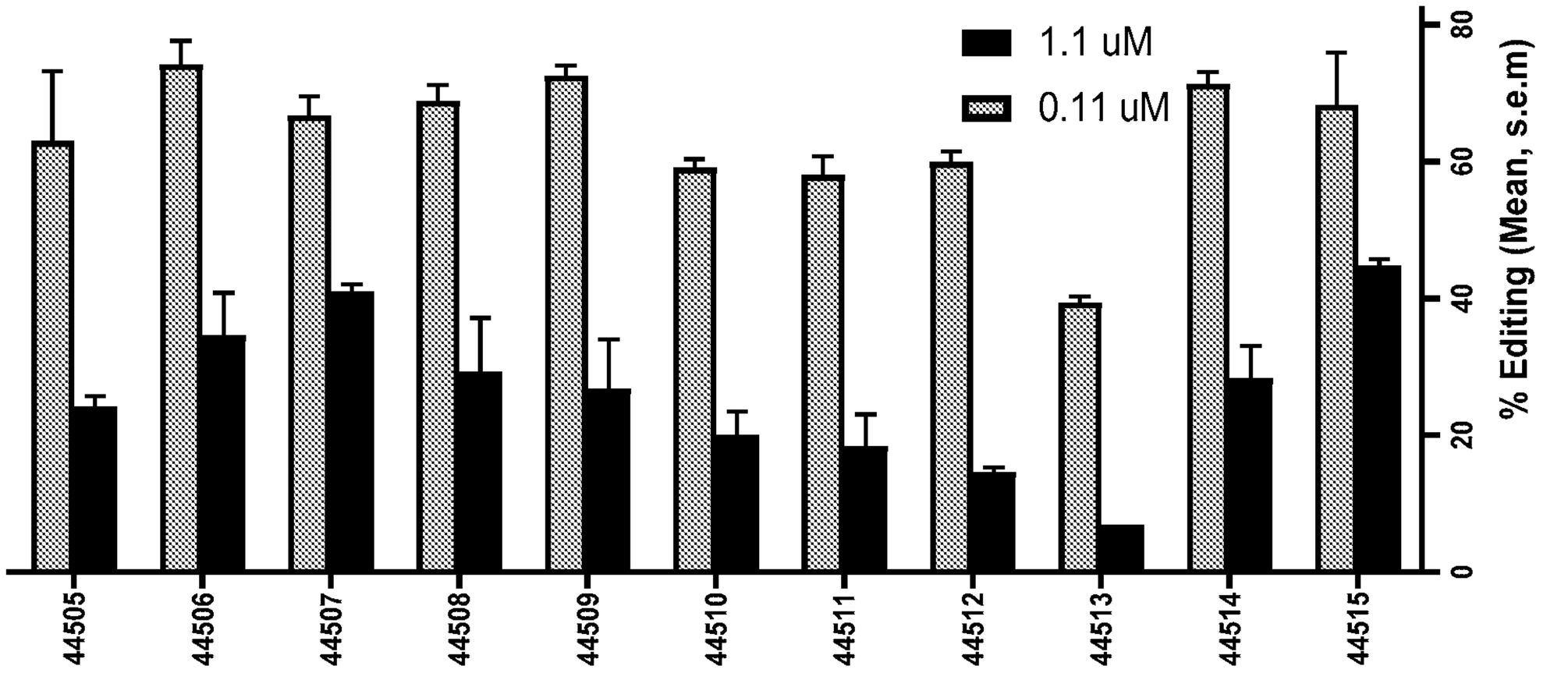


FIG. 63

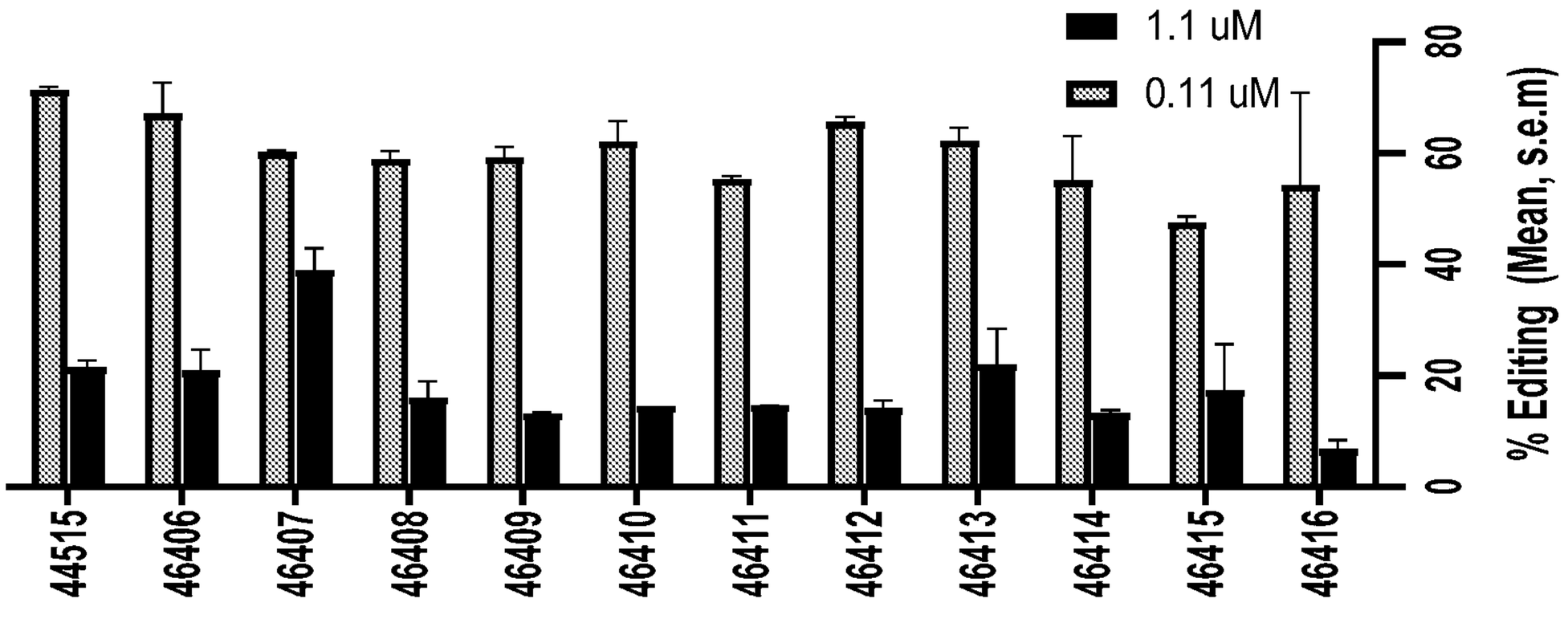


FIG. 64

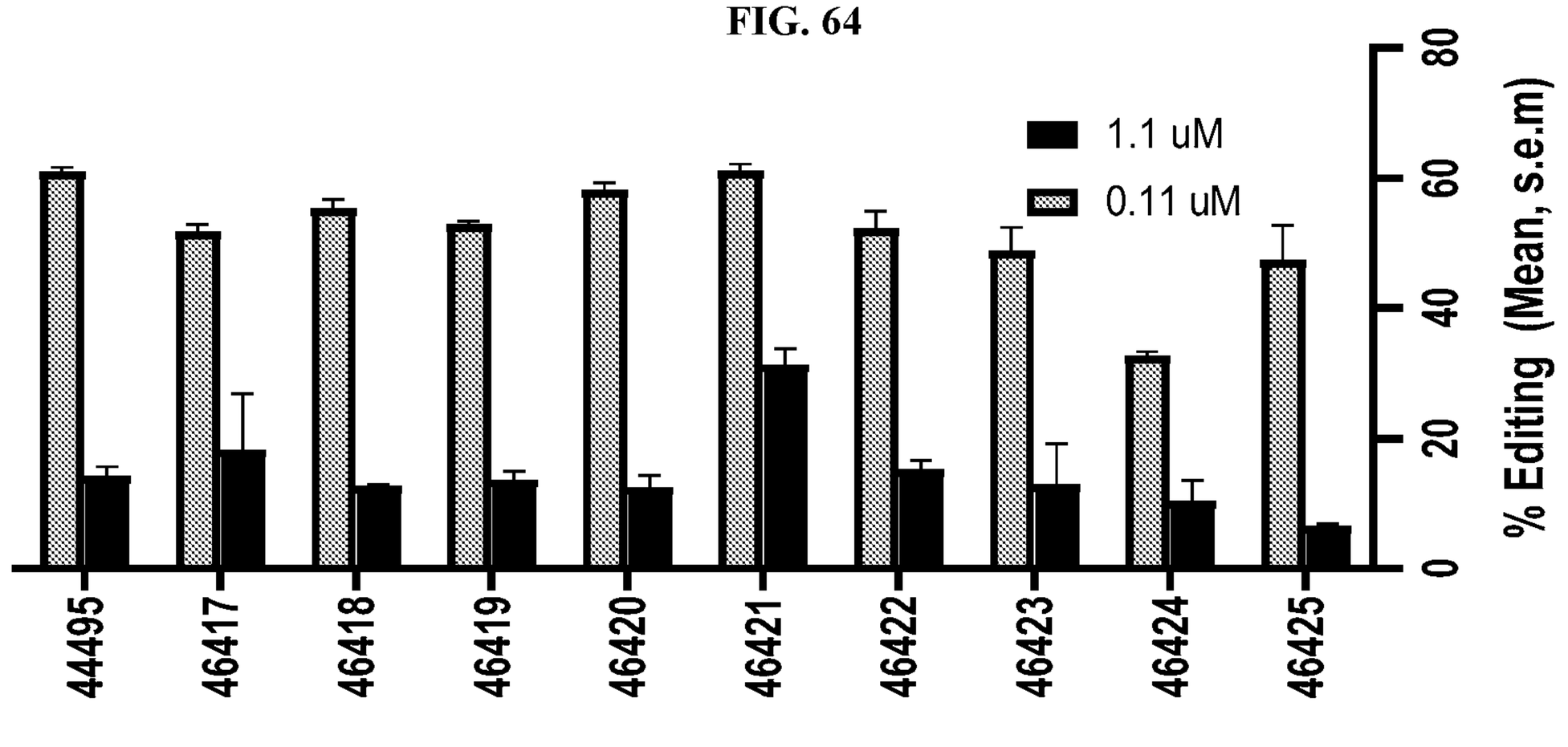


FIG. 65

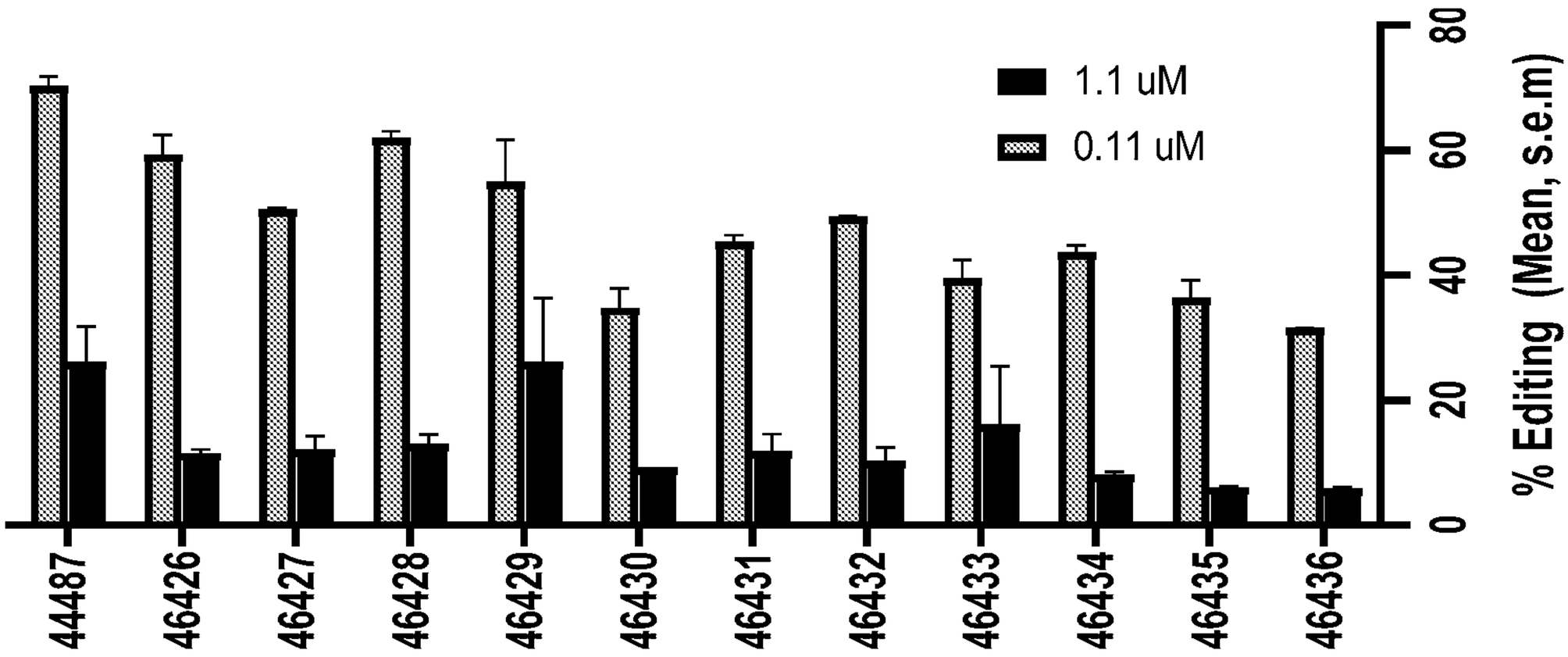


FIG. 66

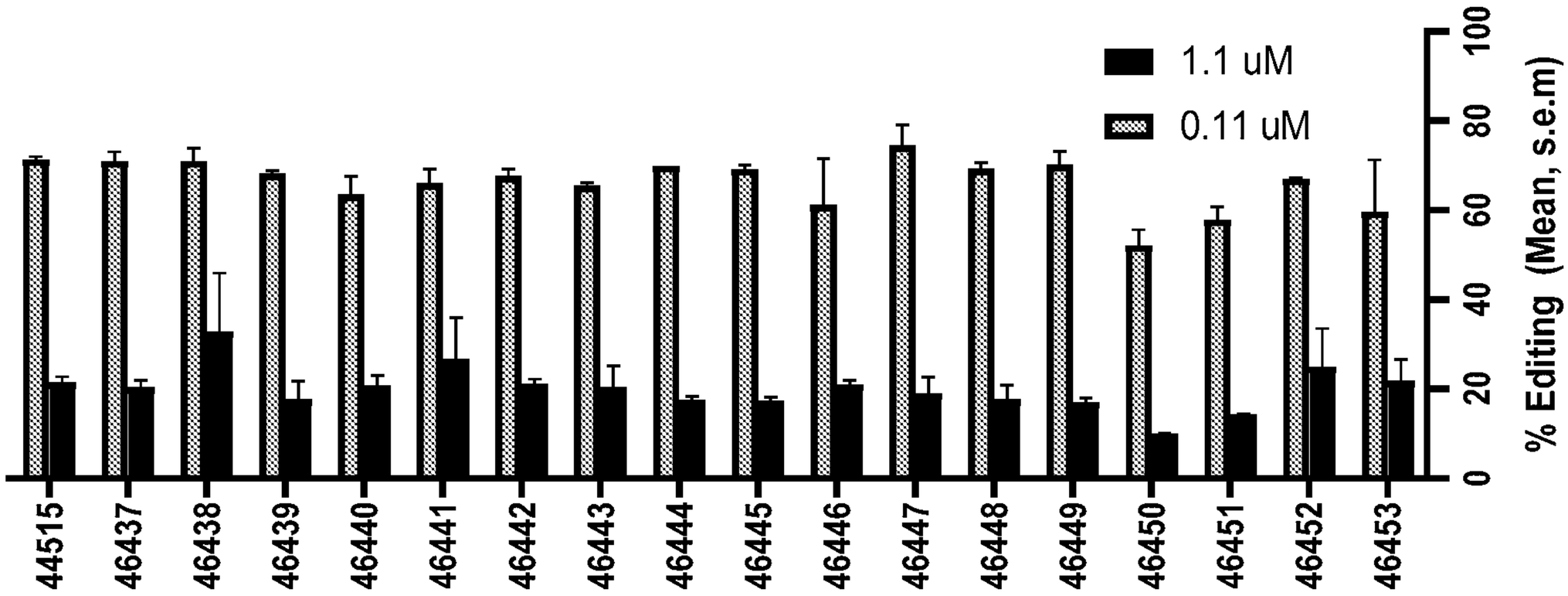


FIG. 67

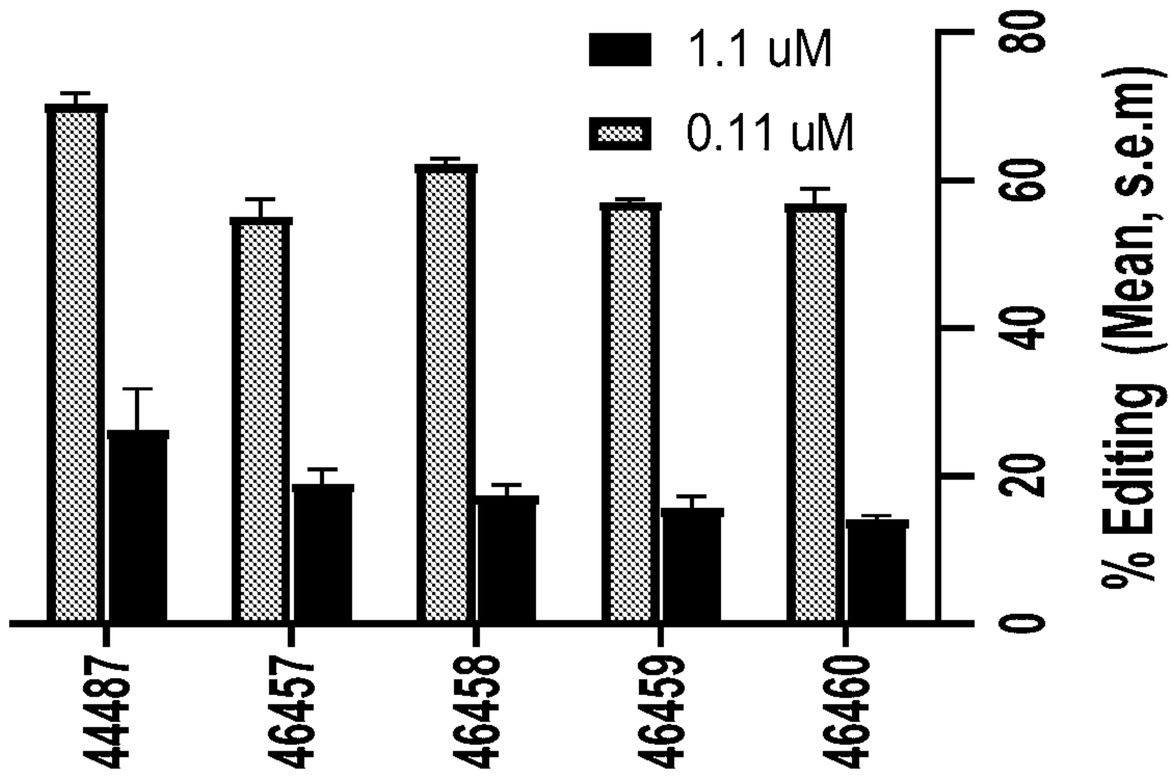


FIG. 68

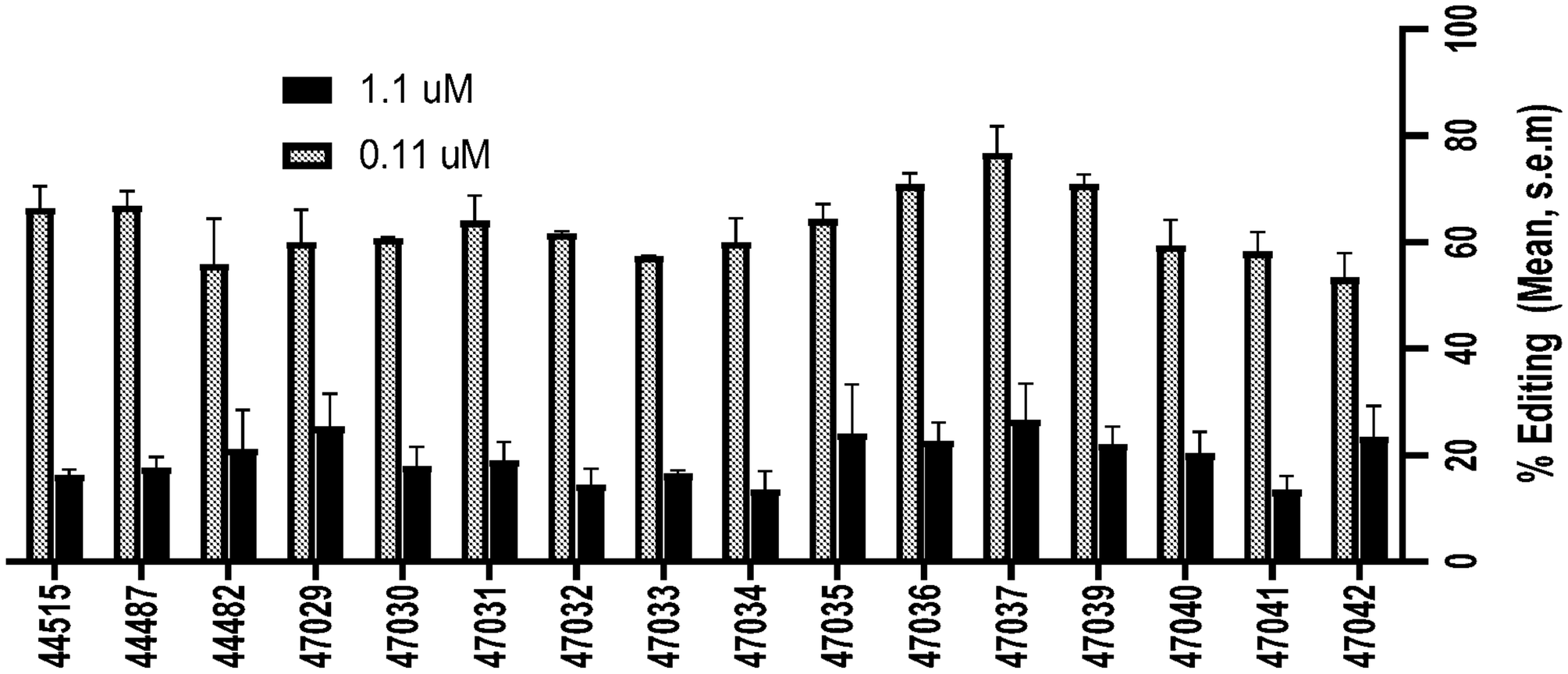


FIG. 69

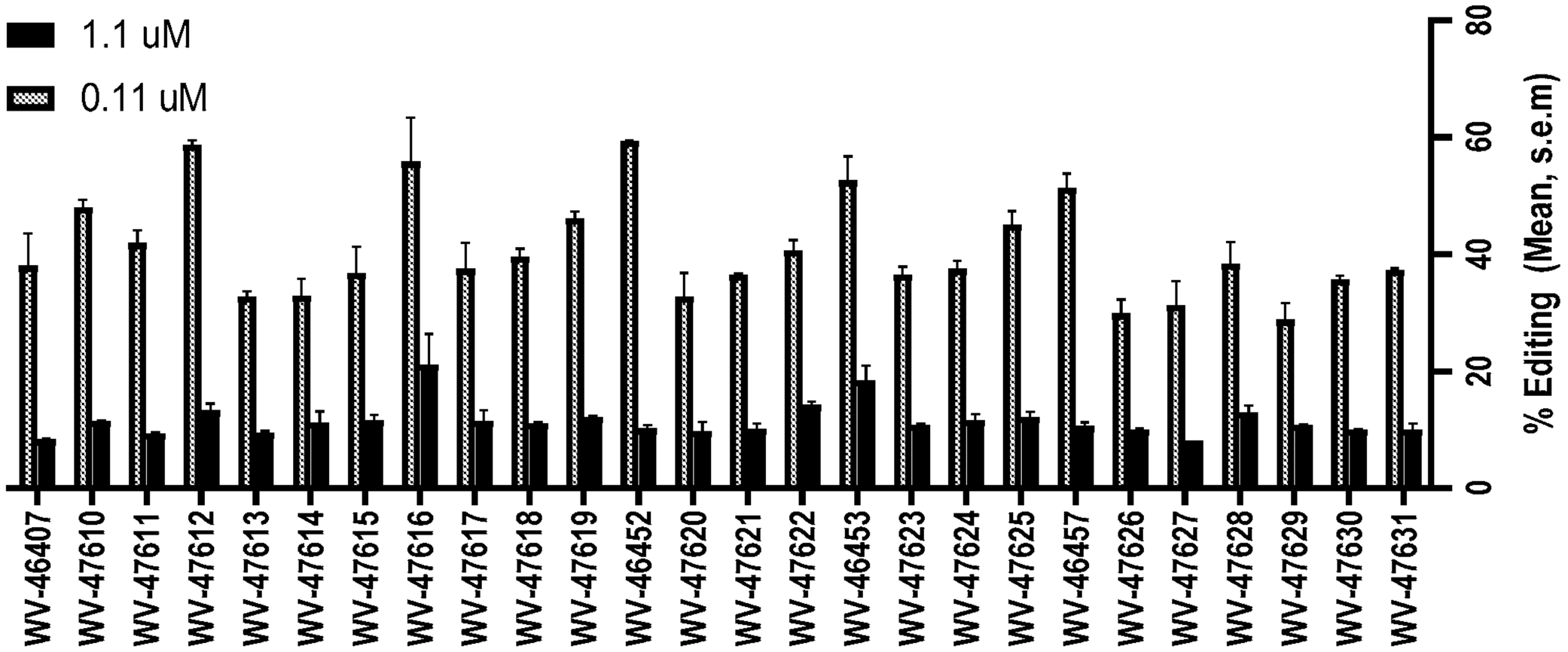


FIG. 70

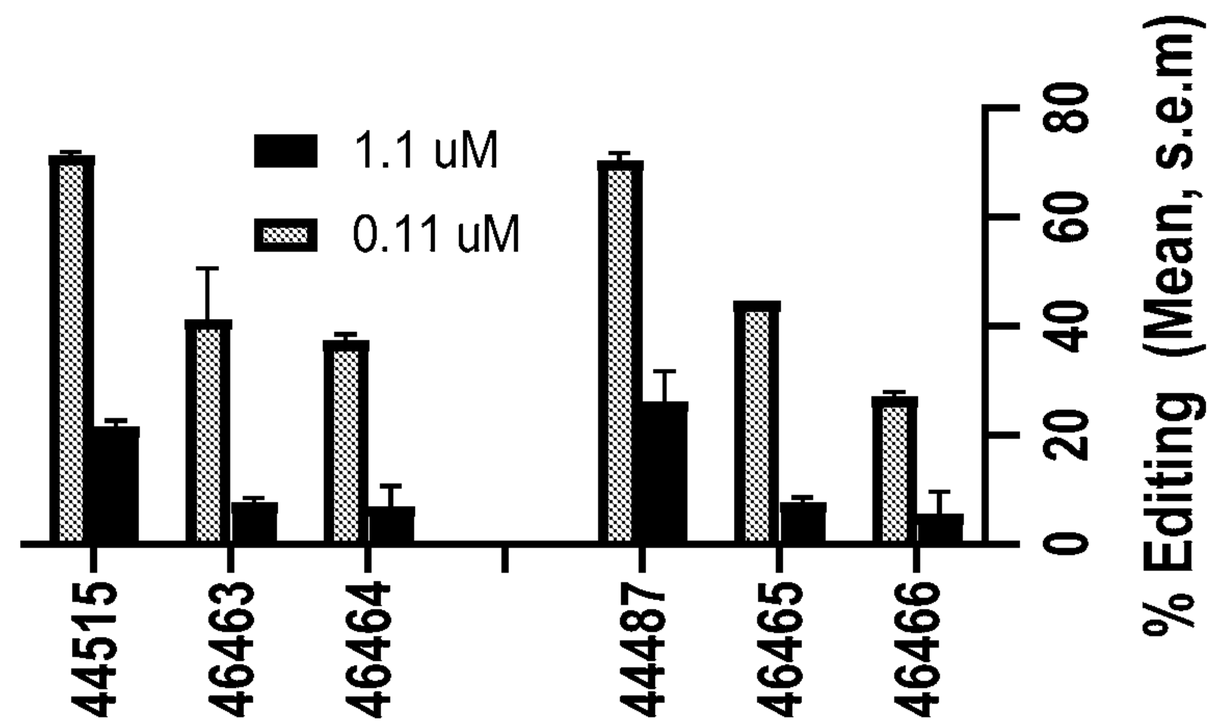


FIG. 71

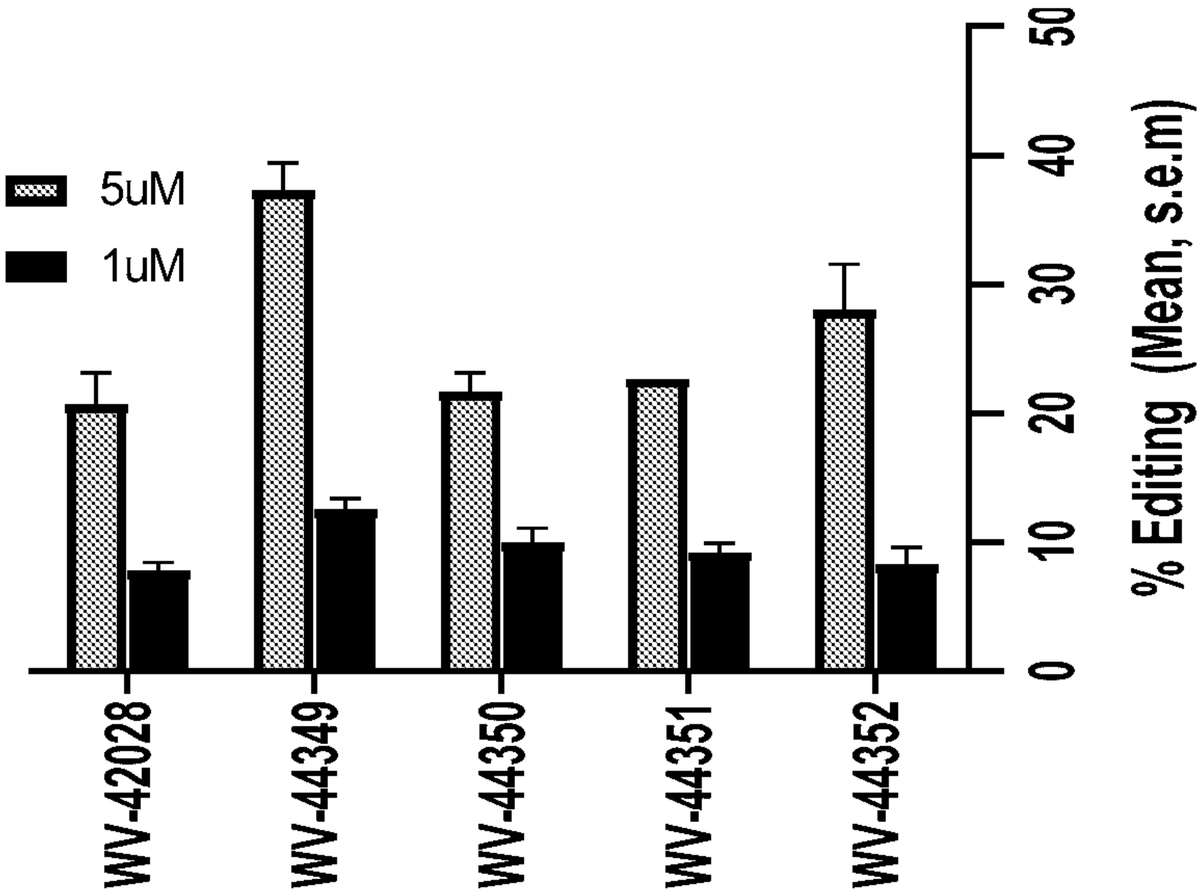


FIG. 72

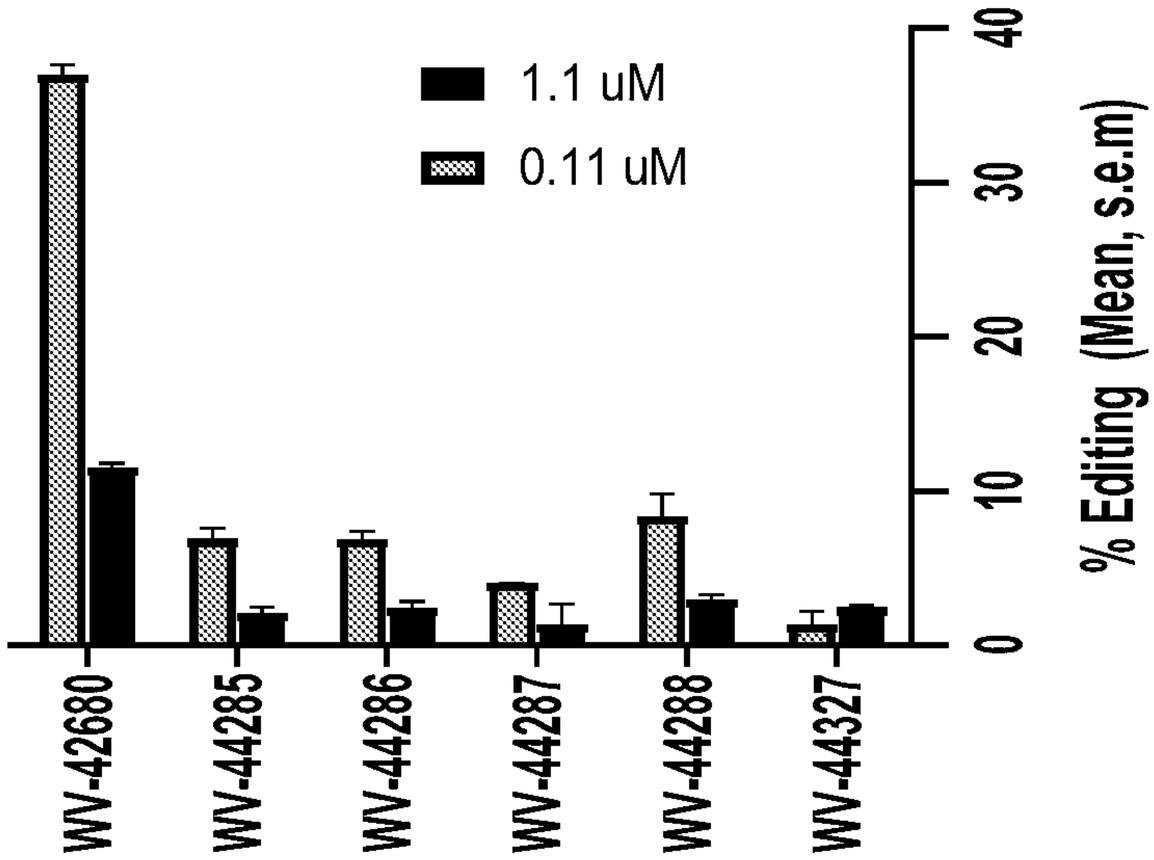


FIG. 73

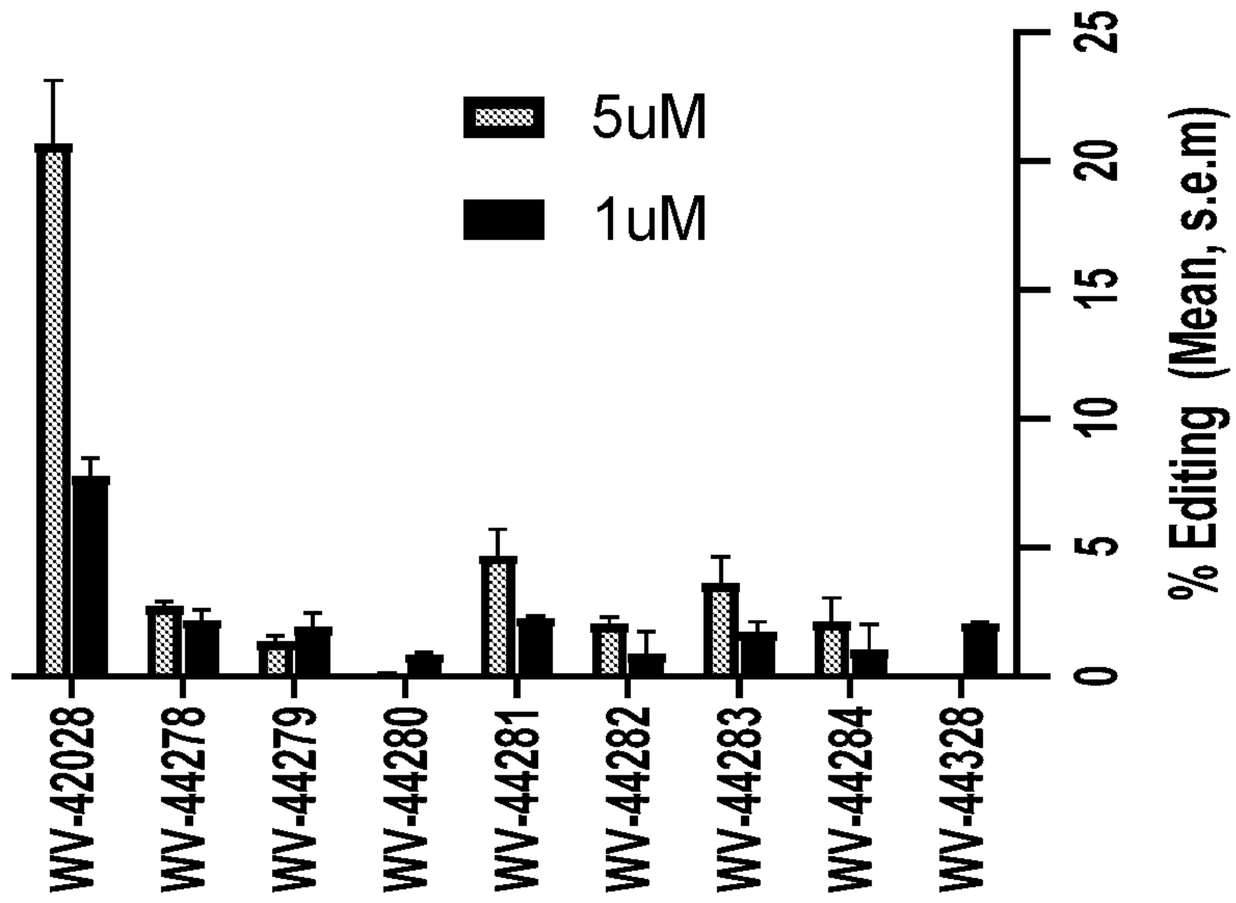


FIG. 74

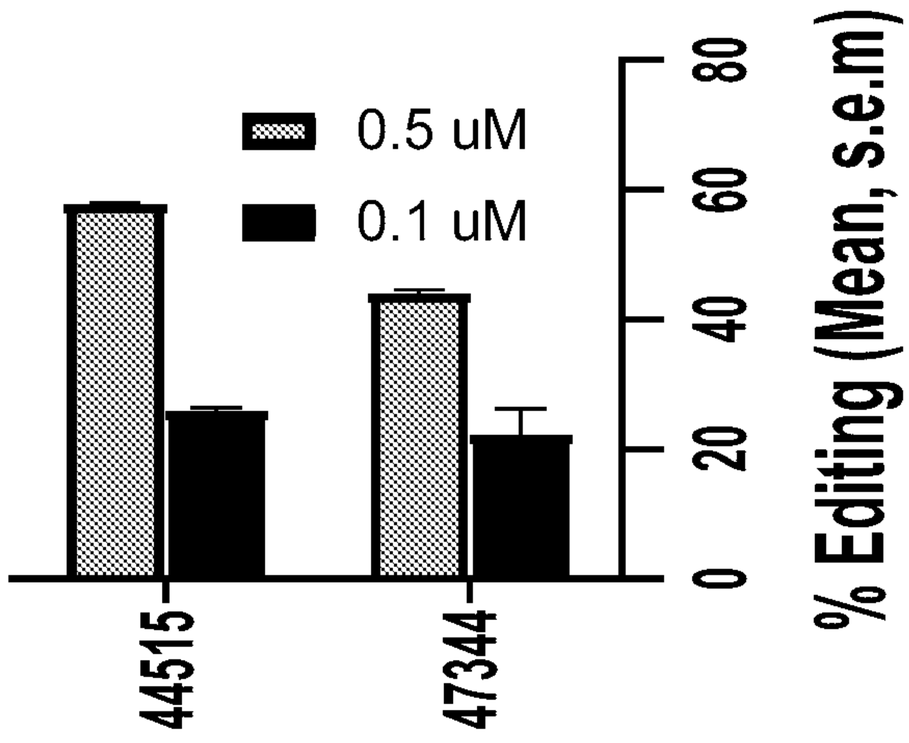


FIG. 75

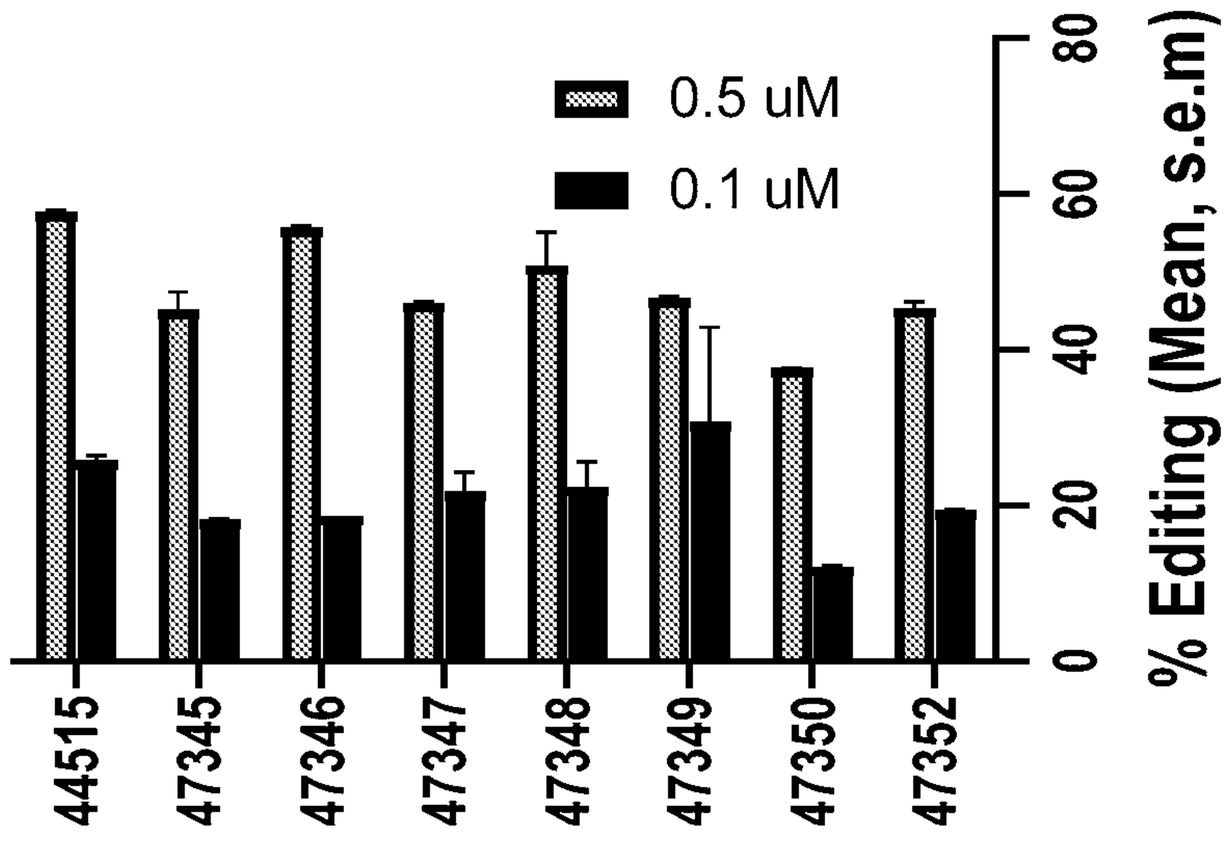


FIG. 76

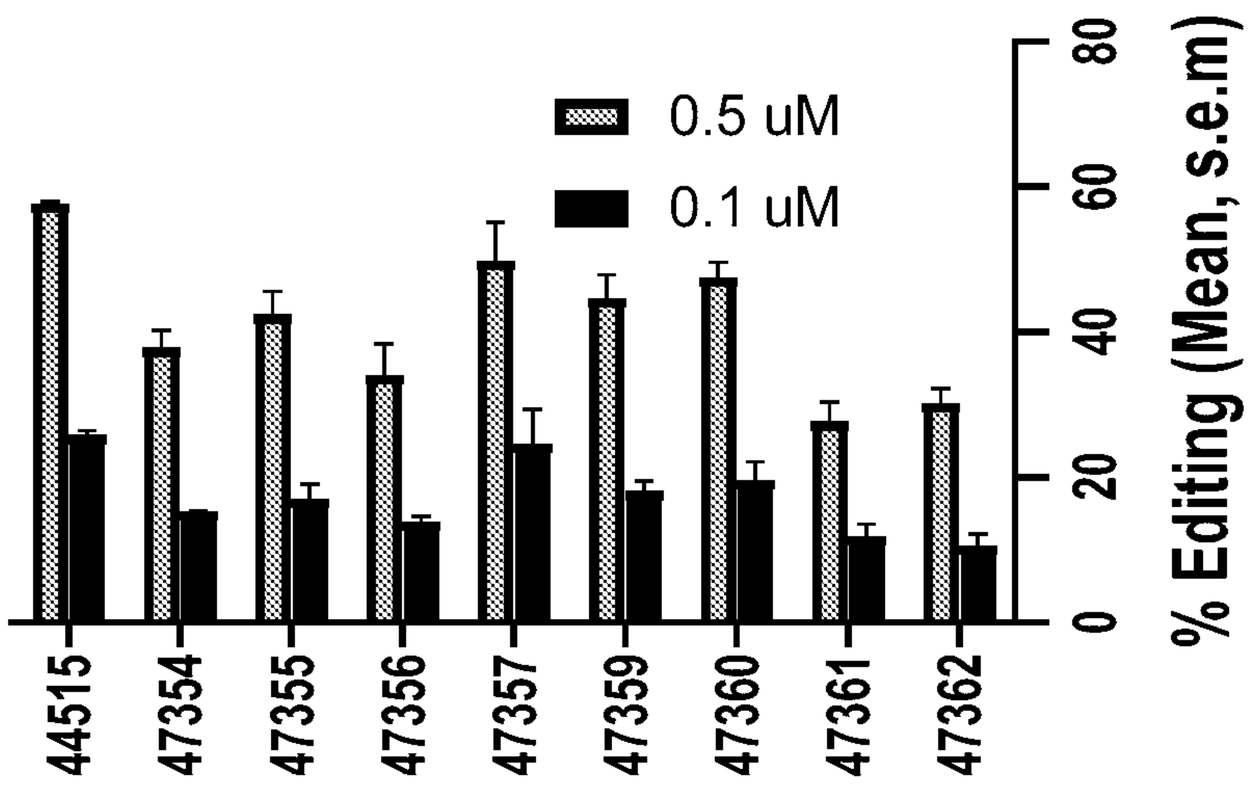


FIG. 77

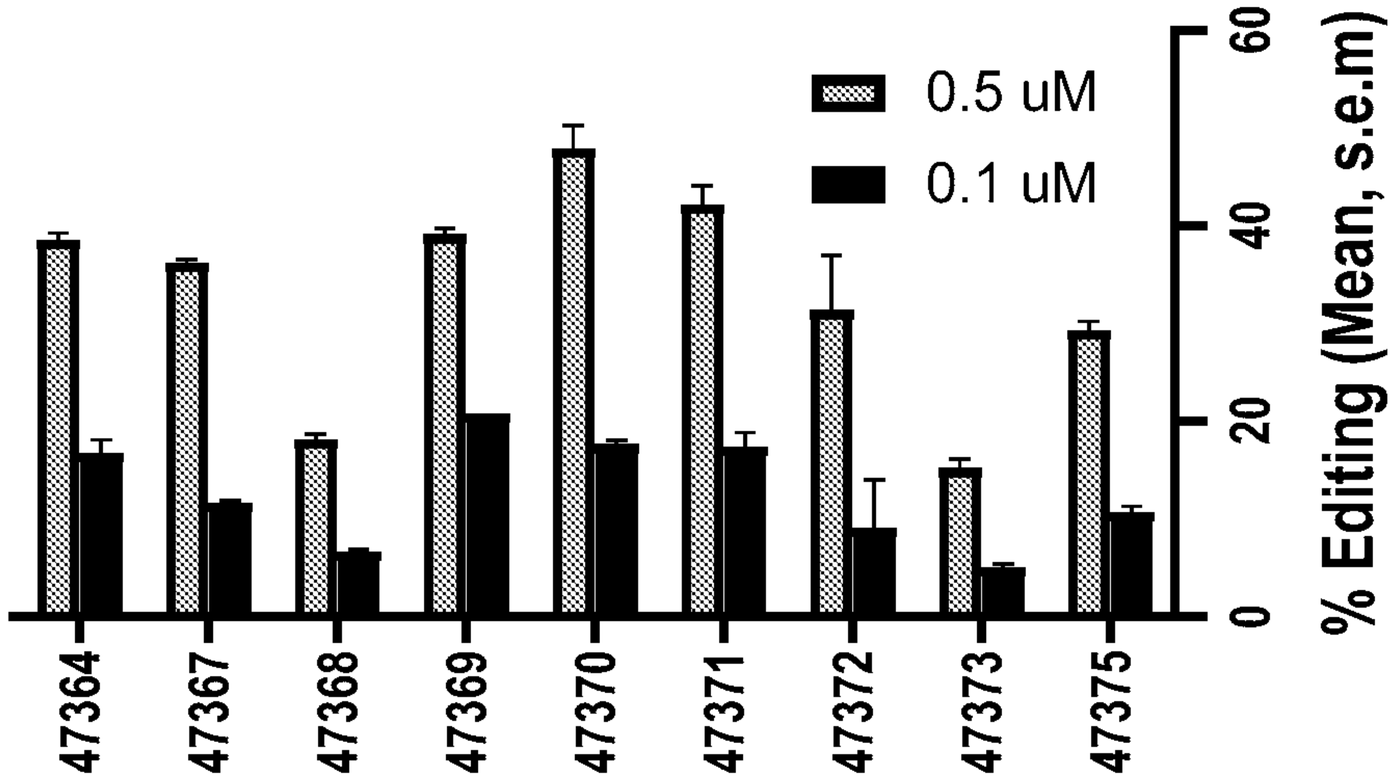


FIG. 78

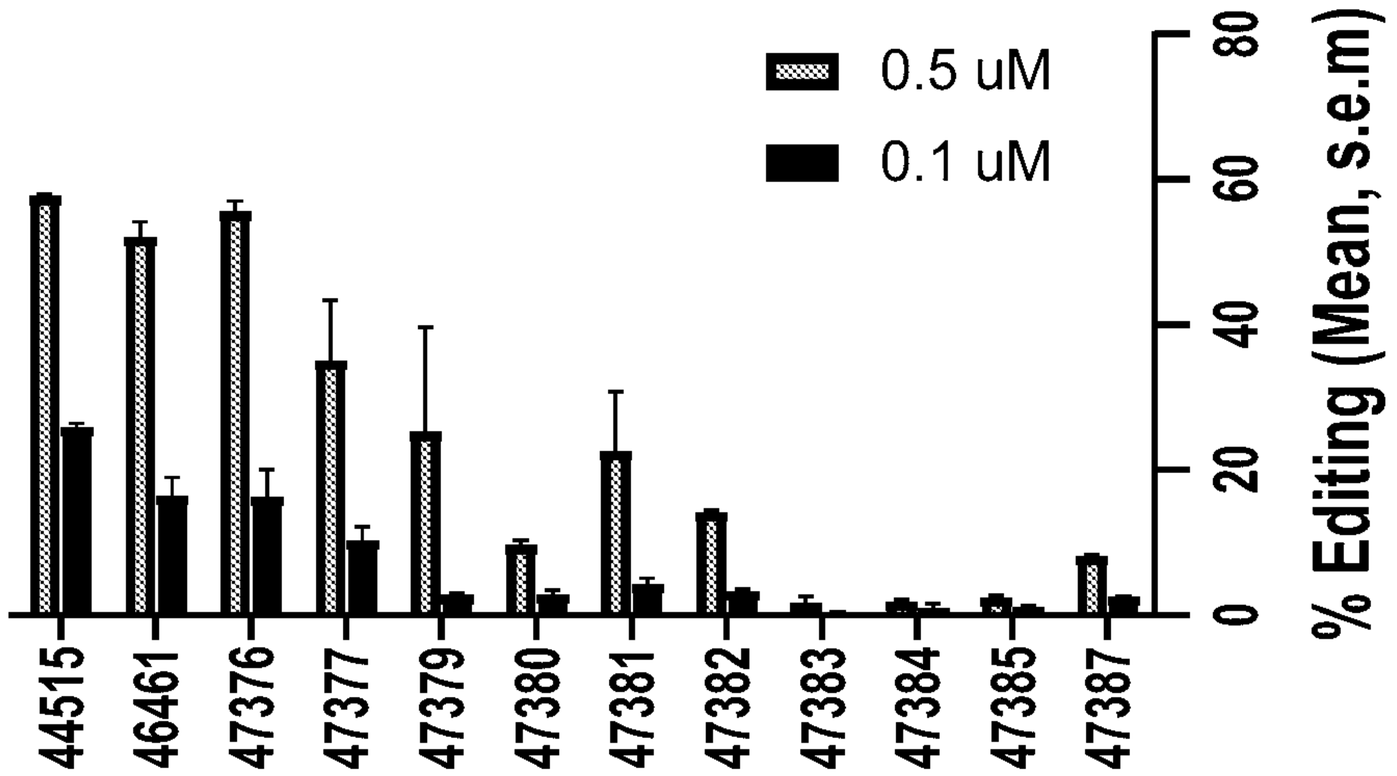


FIG. 79

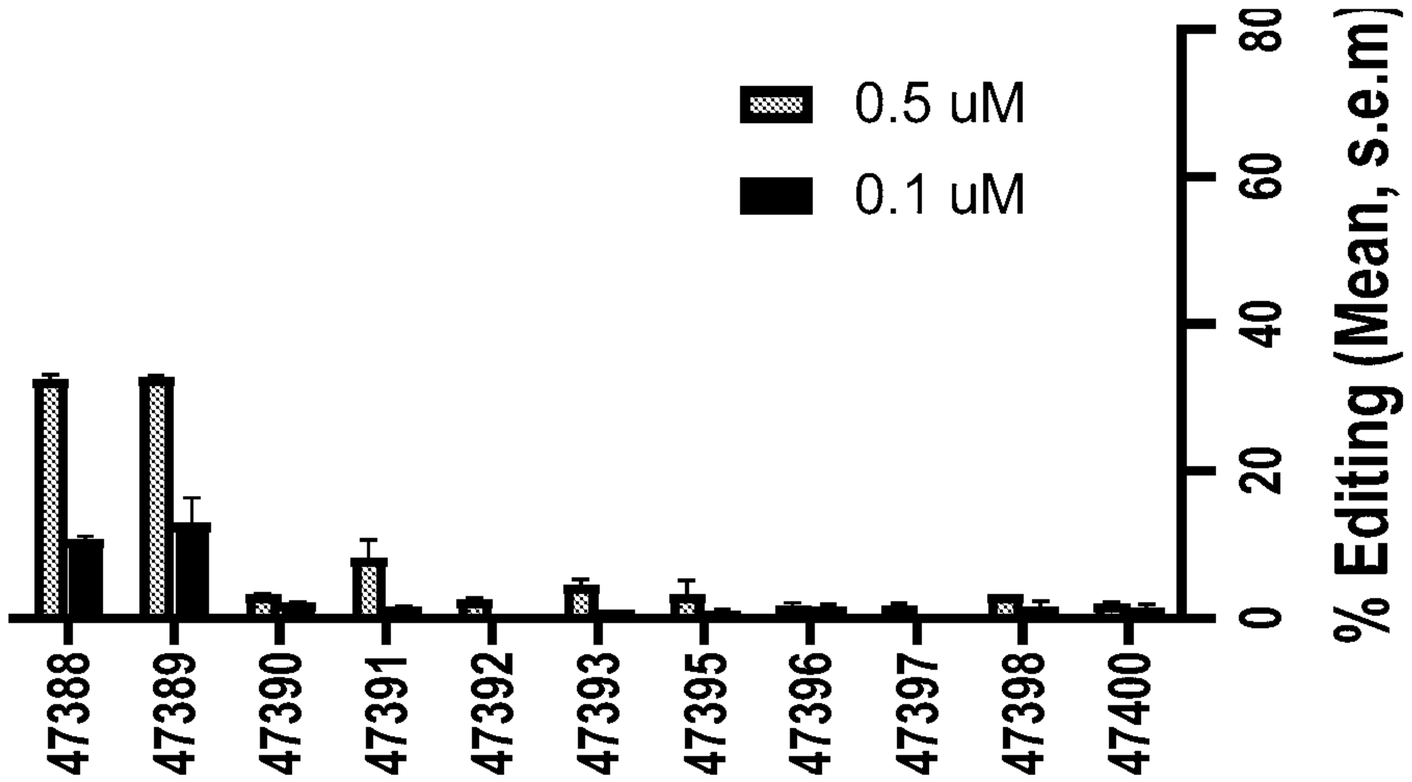


FIG. 80

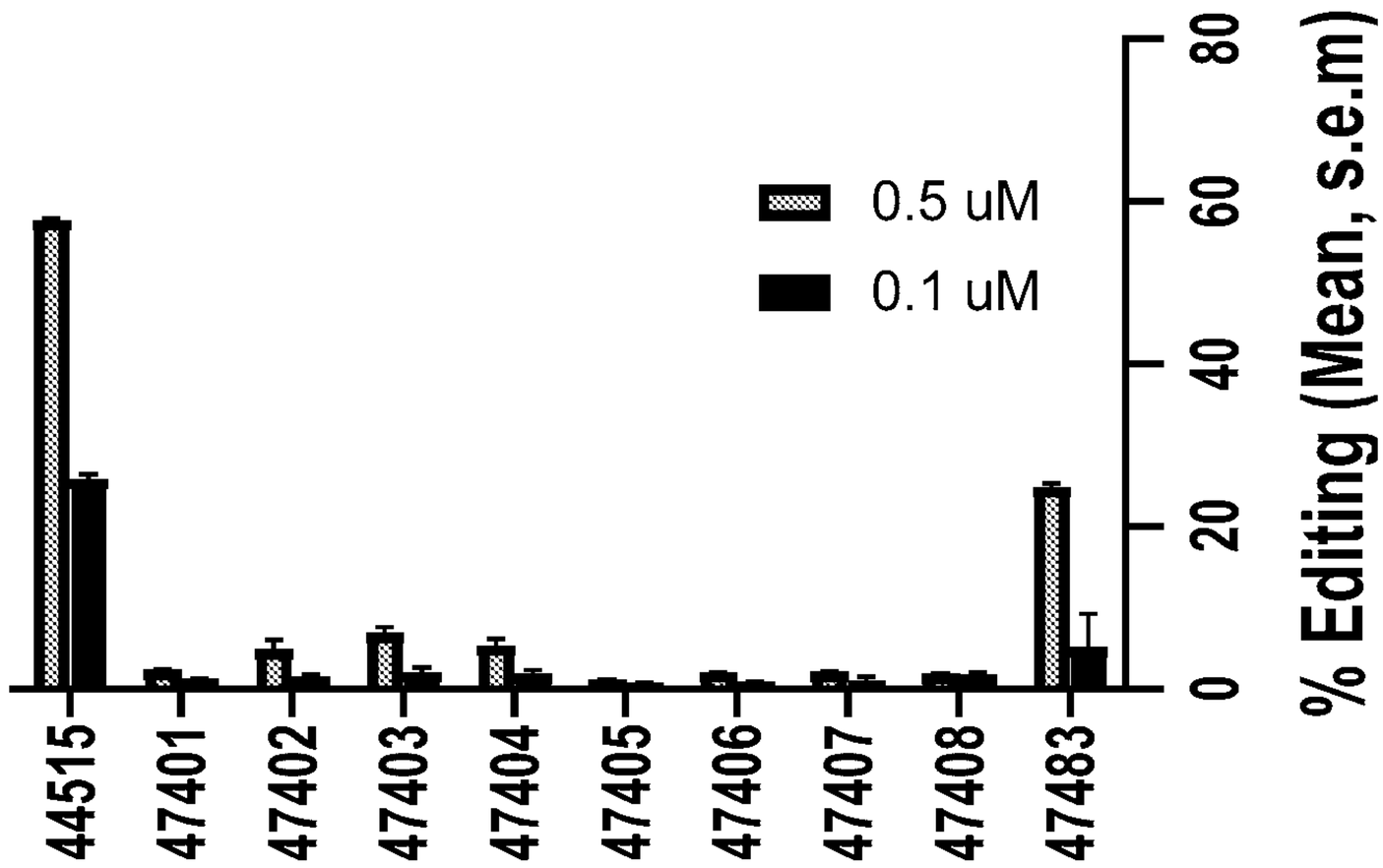


FIG. 81

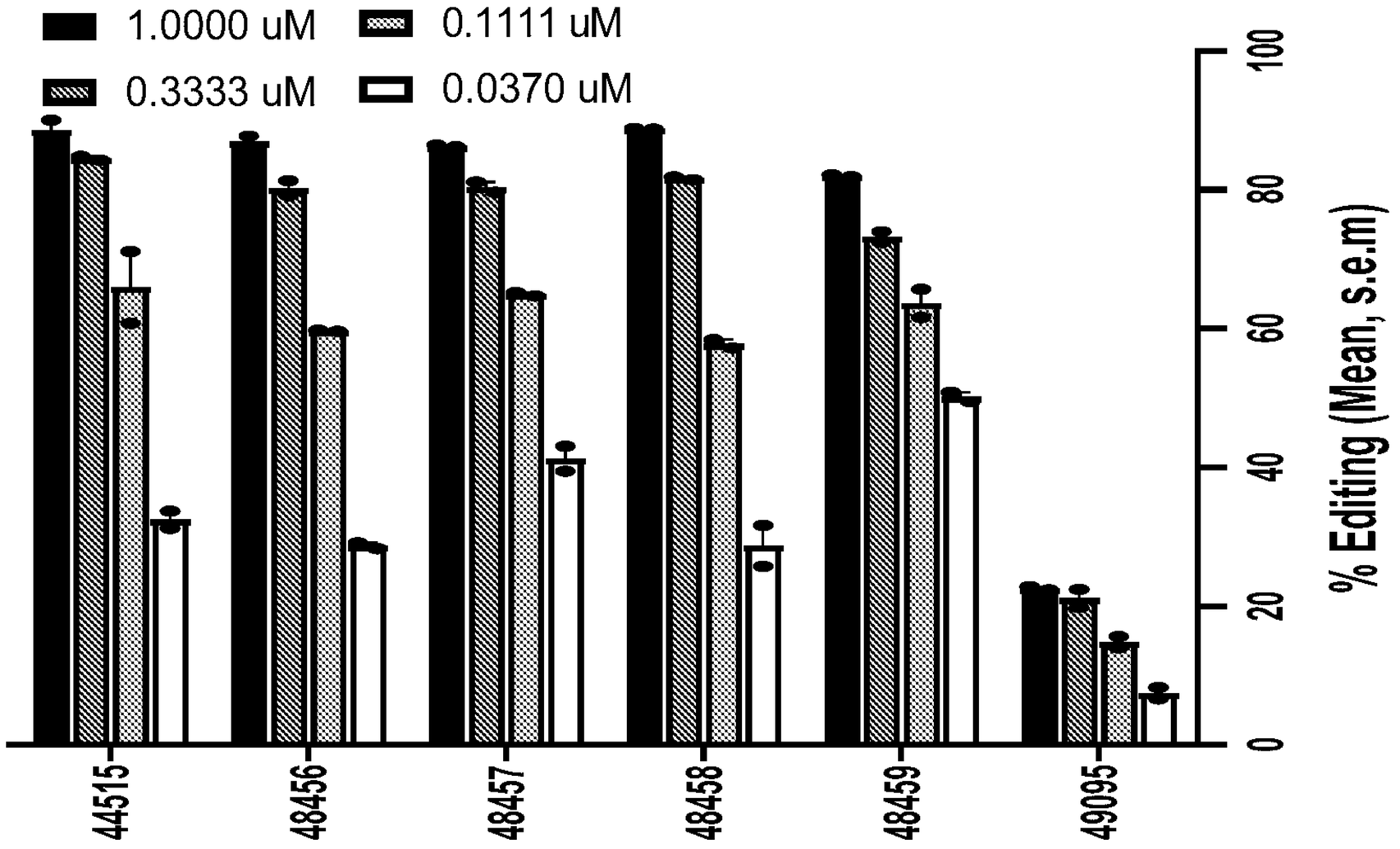


FIG. 82

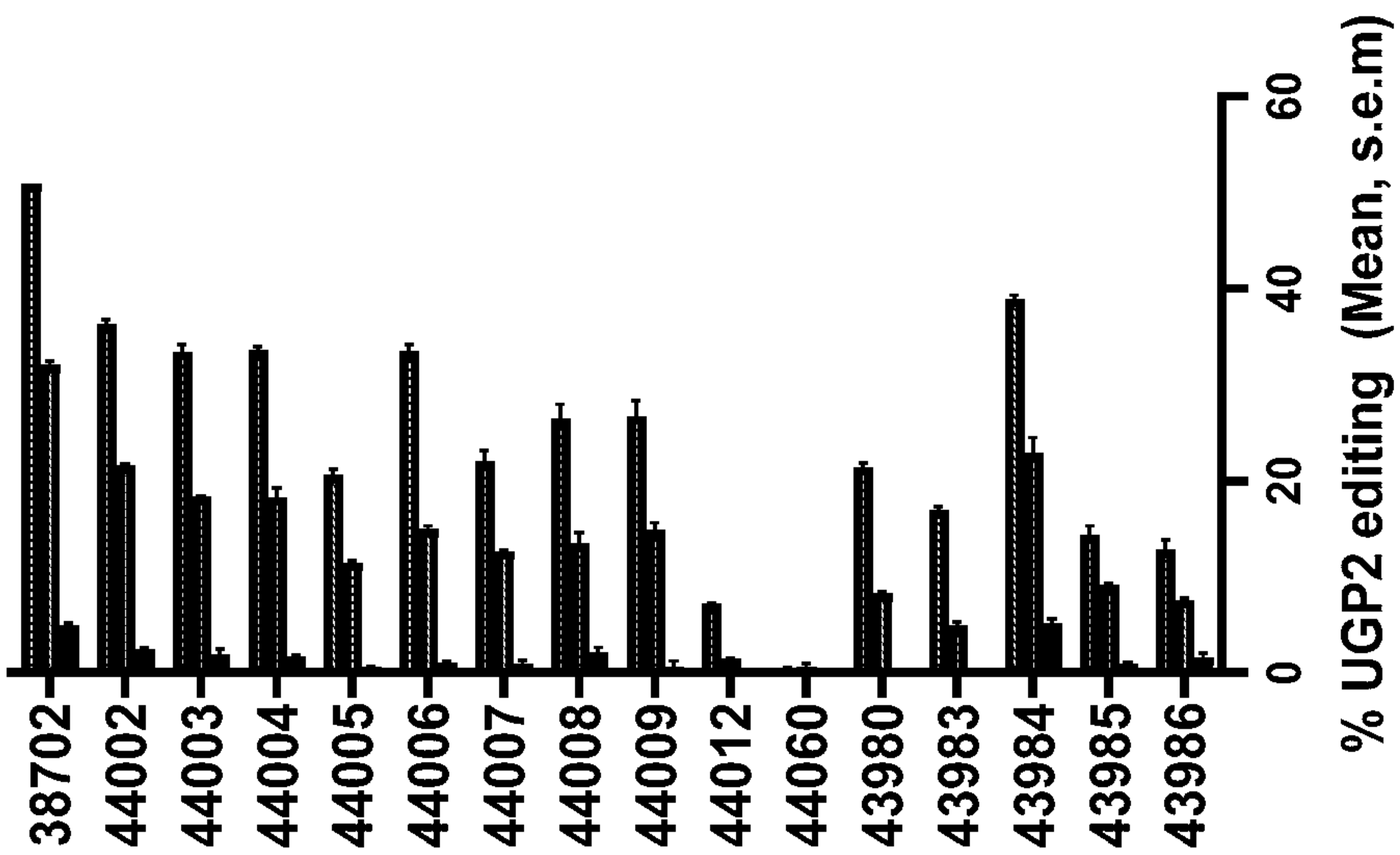


FIG. 83

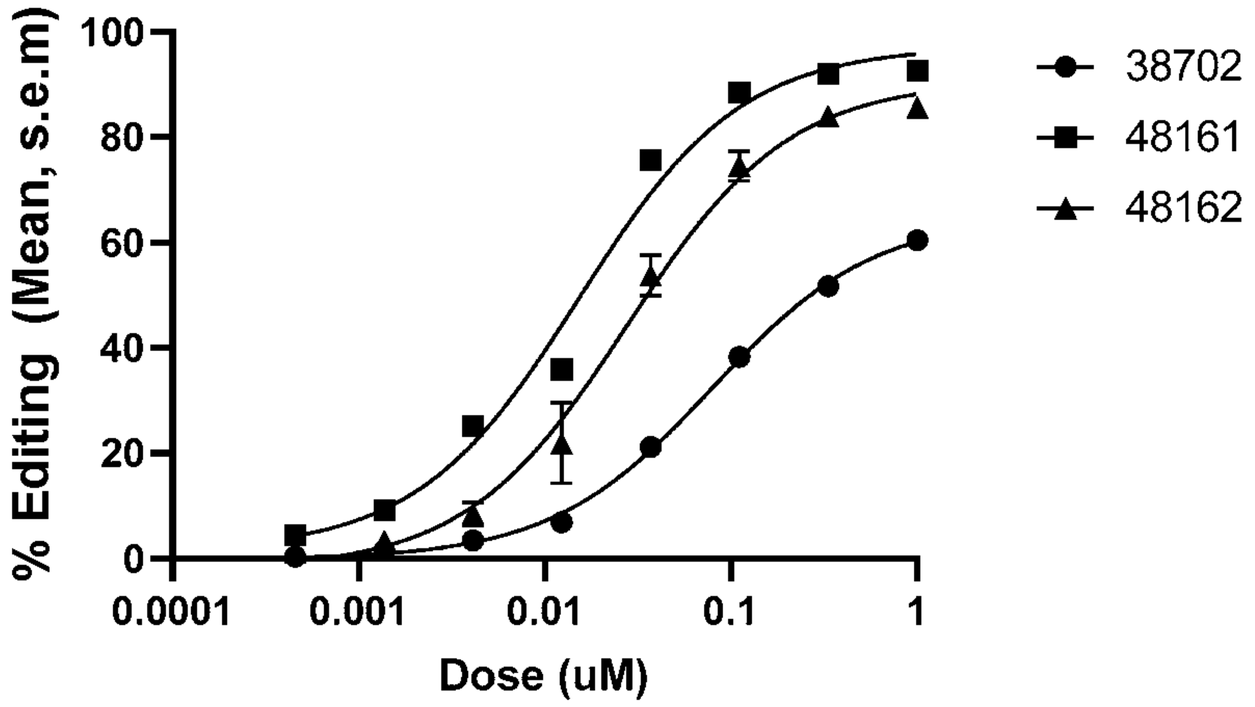


FIG. 84

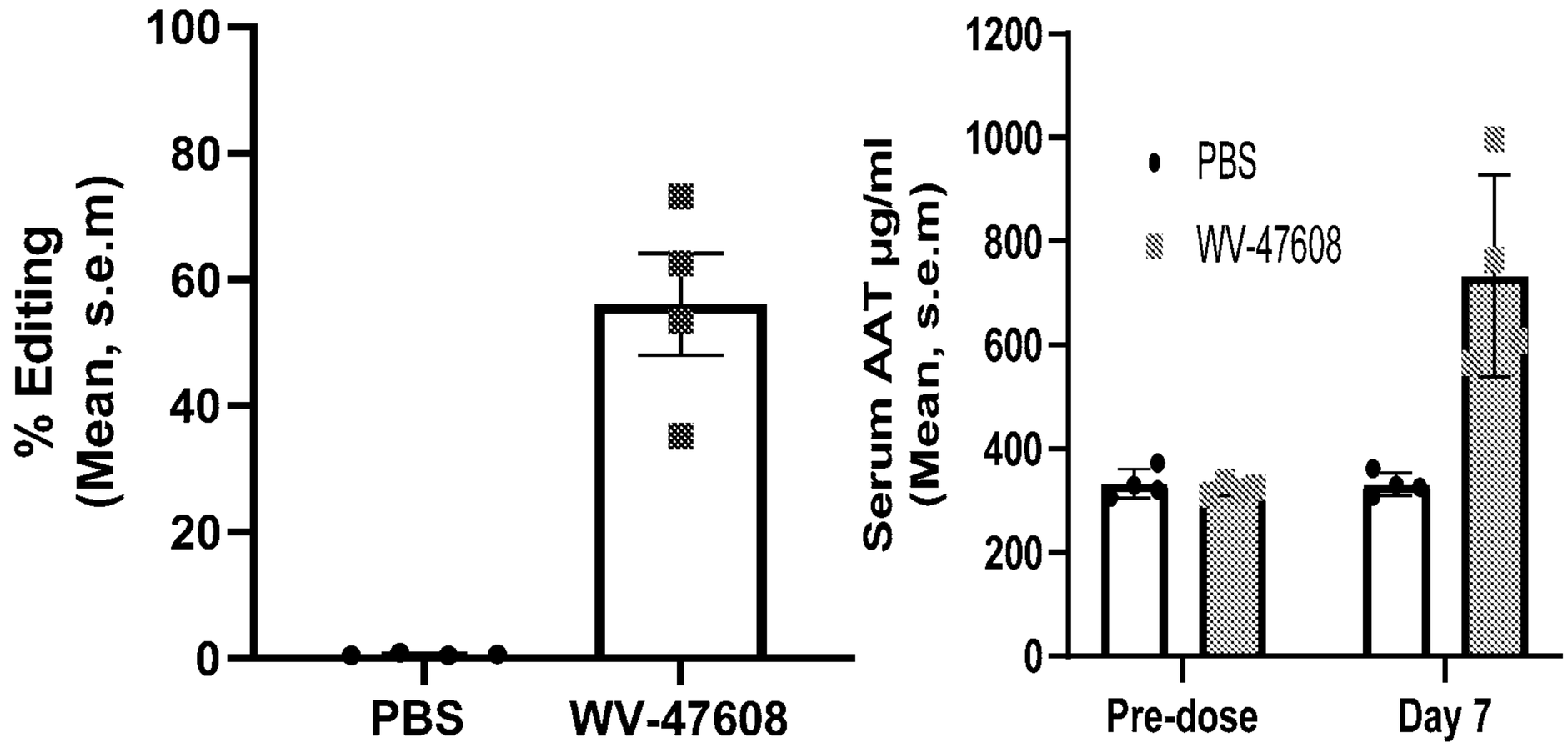

% Editing
(Mean, s.e.m)
100
80
60
40
20
0
PBS
WV-47608
Serum AAT µg/ml
(Mean, s.e.m)
1200
1000
800
600
400
200
0
PBS
WV-47608
Pre-dose
Day 7

FIG. 85

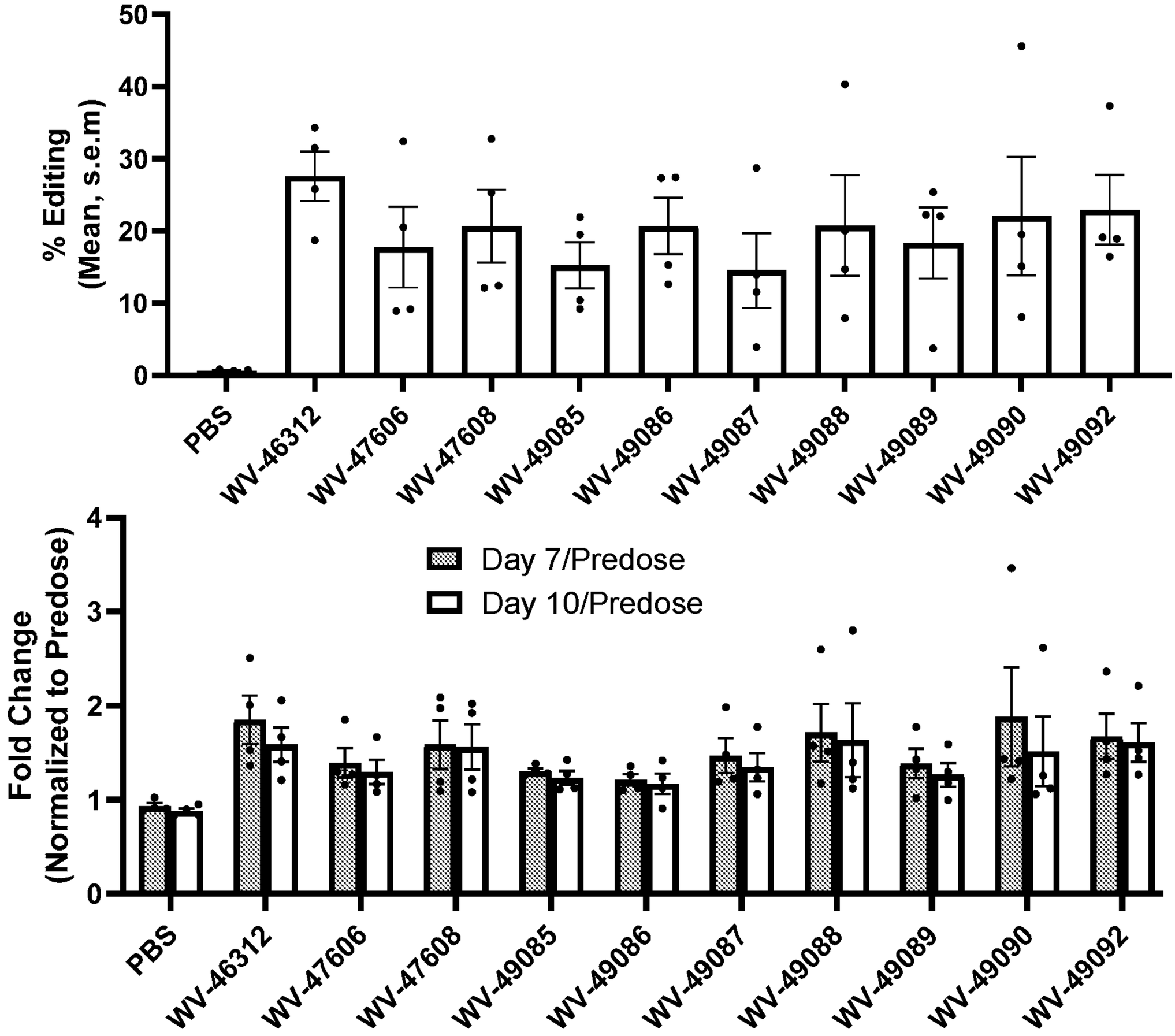

% Editing
(Mean, s.e.m)
50
40
30
20
10
0
PBS
WV-46312
WV-47606
WV-47608
WV-49085
WV-49086
WV-49087
WV-49088
WV-49089
WV-49090
WV-49092
Day 7/Predose
Day 10/Predose
Fold Change
(Normalized to Predose)
4
3
2
1
0
PBS
WV-46312
WV-47606
WV-47608
WV-49085
WV-49086
WV-49087
WV-49088
WV-49089
WV-49090
WV-49092

FIG. 86